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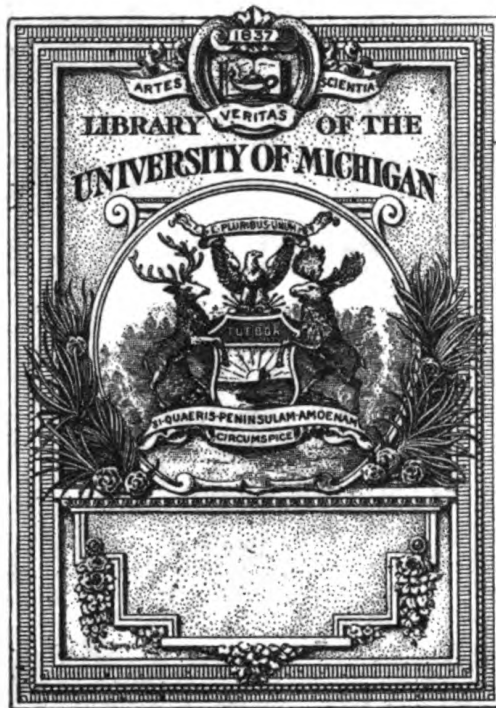
ARCHIVES OF NEUROLOGY

THE PATHOLOGICAL LABORATORY

LONDON COUNTY ASYLUMS

CLAYBURY ESSEX

VOL. III



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ARCHIVES OF NEUROLOGY

FROM

THE PATHOLOGICAL LABORATORY

OF THE

LONDON COUNTY ASYLUMS

CLAYBURY, ESSEX

EDITED BY

FREDERICK WALKER MOTT, F.R.S., M.D., F.R.C.P.

*Director of the Laboratory and Pathologist to the London County Asylums ;
Physician to Charing Cross Hospital*

VOL. III.

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PREFACE.

IN the two preceding volumes of the Archives of Neurology from the Pathological Laboratory of the London County Asylums, syphilis as the direct cause of general paralysis of the insane and as a direct and indirect cause of organic brain disease, was the main subject of investigation. In this volume are described the changes in the nervous system caused by chronic trypanosome infections, such as sleeping sickness and dourine; and their similarity to syphilis is discussed. This is of interest because syphilis is now regarded as a protozoal disease caused by the *Treponema pallida*, an organism closely allied to a trypanosome. Several articles, including one by Dr. Georg Eisath, are devoted to this subject, and I desire here to acknowledge my indebtedness to the Colonial Office and the Royal Society for permission to use the illustrations contained in my Report, which is the Seventh of the Sleeping Sickness Commission of the Royal Society.

The subject of alcoholism in its relation to disease of body and mind, as studied in hospital and asylum practice, occupies a prominent place among the contributions. While recognising the fact that if we could eliminate the effects of alcoholism and syphilis, we might reduce the total number of admissions to the asylums by 25 to 30 per cent., and allowing that a certain number of patients may lose their reason on account of other toxæmic conditions or from mental shock, grief or other emotional and moral causes, still I am convinced that the most important cause of insanity is an inborn mental deficiency or instability. What we term the cause may be a coefficient, and often

merely serves as the spark which falls into the explosive matter.

Many subjects relating to the structure, functions, development and evolution of the brain in man and animals are dealt with in the pages of this book, notably a valuable original contribution by my late assistant, Dr. Watson, concerning the structure of the brains of the Insectivora, an abstract of which was published in *The Proceedings of the Royal Society*; also the Bowman Lecture for the year 1904, which I had the honour of giving, upon the progressive evolution of the visual cortex in man. The extension and amplification of this work to the convolucional pattern of the parieto-occipital region in lunatics and low types of human beings has led me to the conclusion that a large number of the insane have a defective convolucional pattern as compared with the normal average; especially is this deficiency manifest in the parietal lobe. Several other papers deal with the structure and functions of the brain as exhibited by the effects of pathological processes. I also call attention to the description of the brains of seven Chinamen by Mr. Harper.

The subject of poisoning by illuminating gas may possibly be considered irrelevant to the pathology of insanity, but the frequent deaths which now occur owing to the admixture of carburetted water gas, makes the subject of the changes in the nervous system of considerable importance and worthy of investigation. I wish here to take the opportunity of thanking Dr. F. T. Oliver for the use of four of the blocks made from photographs which I lent him to illustrate his Harben Lectures.

A good deal of work has been done in the laboratory by Dr. Waldemar Koch and my assistant, Mr. Sidney Mann, on the chemistry of the brain in healthy and diseased conditions; this subject, of necessity, is extremely difficult and complex, and the papers are more or less preliminary to further investigations.

A research has been undertaken by Professor Halliburton and myself on the suprarenal glands in relation to the possibility of their disorganisation being associated with

some form of insanity. The results, although not barren, from this point of view were, unfortunately, negative.

The technical scholarships which were instituted some years ago have been abandoned owing to the legal decision that "research is not technical education"; the funds of the Board of Technical Education of the London County Council therefore could not be allocated for this purpose. Absence of such workers has reduced the output of new work from the laboratory. I have, however, published two theses written for the M.D.(Cantab.), by Dr. Bodington and Dr. Ascherson. The former is a careful and painstaking research on the changes in the blood in general paralysis; and the latter is a valuable monograph based largely on hospital experience upon the mental state in chronic alcoholism.

It is hoped that in the future more officers in the service of the Asylums Committee will investigate the causation, psychology, clinical symptomatology and pathological anatomy of mental diseases and submit their results as theses for university degrees. Such work would be welcomed in the Archives of Neurology and Psychiatry as they were forthcoming; and it is hoped by this means that sufficient research work will be produced to enable an annual volume to be published.

I am at present engaged in organising a systematic research concerning the relation of certain types of insanity to hereditary predisposition.

Another fruitful field of study in Psychiatry would be those early cases of uncertifiable mental affection termed neurasthenia, psychasthenia, obsession, mild impulsive mania, melancholia, hysteria and hypochondria, which in many instances are really the prodromal stages of a pronounced and permanent mental disorder. The poorer patients suffering with these conditions first come into the hands of the practitioner, the dispensary or infirmary doctor, and the out-patient physician at the general or special hospitals. The better class patients are sent by the practitioner to the neurologist; the generality of the poorer patients, and sometimes the better class patients, are

regarded by the medical man who has had no training in psychology as of little medical interest (for such patients do not, as a rule, benefit by drugs), and he finds it a wearisome task to listen to their story, to ascertain their inborn tendencies, and to find out the truth of what has happened to account for their strange conduct indicative of their not feeling, thinking and acting in accordance with the general usages of their social surroundings, and yet such patients may not be so anti-social as to be certifiable. Such cases are often in the hopeful and curable stage, and these, if studied carefully by trained medico-psychologists, could not fail to yield valuable results in regard to our knowledge of the causation, prevention and cure of insanity. Moreover, when the cases are followed up systematically, they would throw much light on prognosis in similar cases. The majority of cases which are admitted to the asylum have long passed the hopeful stage; still there are a certain number of early curable cases, and these, I maintain, would sometimes be much better if they had not been certified or sent to associate with chronic lunatics.

In connection with this subject, I will quote from a recent valuable work on Psychiatry, by Dr. Paton. After calling attention to the national importance of the investigation of the acquired and inborn causes of insanity by psychological, sociological, chemico-physical and anatomo-pathological methods, he remarks: "Fortunate would be the community in which there was a fully-equipped and well-organised psychiatric clinic, under the control of a University, and dedicated to the solution of such problems. The mere existence of such an institution would indicate that people were as much interested in endeavouring to increase the public sanity, as they are in the results of exploration in the uttermost parts of the earth or in the discovery of a new star."

The scheme of the London County Council for Receiving Houses would probably include the establishment of an acute Hospital for the investigation and treatment of curable mental cases, to which a clinic might with advantage be attached. Hereby, post-graduate teaching would

be encouraged, and the better knowledge and early treatment of insanity would certainly prove of great economic advantage. If suitable post-graduate training in medicopsychology and neuro-pathology were established, doubtless the universities and licensing bodies might be induced to establish a diploma, very much on the lines of the Diploma of Public Health, which has largely contributed to raise the science of Public Health to the high position it now holds, thus conferring an inestimable benefit on the nation.

The delay in the publication of the present volume has been partly due to my long illness two years ago, and to three unavoidable changes in my assistants which has seriously interfered with the necessary leisure for compiling this work. Dr. J. W. Evans, a most promising scientific officer, much to my regret, died of blood poisoning shortly after he was appointed. He was most assiduous in his duties, but had not time to complete any work; I have, however, published his notes of two cases of Raynaud's disease.

In conclusion, I wish to express my obligations to my assistant, Dr. J. P. Candler, for the help which he has given me in this volume by his careful statistical enquiry concerning the *post-mortem* records on the alcohol question, and for his review of the subject of dysentery in asylums.

I also desire to thank Miss A. Kelley for the excellent drawings which illustrate many of the communications, and my assistant, Mr. Geary, for technical skill in preparing the photo-micrographs and microscopic preparations.

F. W. MOTT.

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ARCHIVES OF NEUROLOGY
OF THE PATHOLOGICAL LABORATORY
OF THE
LONDON COUNTY ASYLUMS.

THE PROGRESSIVE EVOLUTION OF THE STRUCTURE AND FUNCTIONS OF THE VISUAL CORTEX IN MAMMALIA.

*Being the Bowman Lecture, delivered on November 4, 1904, and published in the "Transactions of the Ophthalmological Society," January, 1905.**

BY F. W. MOTT, M.D., F.R.S.

Physician to the Charing Cross Hospital and Pathologist to the Asylums of the London County Council.

MR. PRESIDENT AND GENTLEMEN,—Allow me to thank you for the great honour which the Ophthalmological Society has conferred upon me by requesting me to deliver this lecture, which was instituted in commemoration of a great physiologist and ophthalmic surgeon whose discoveries are permanently associated with his name. I must also tender my apologies for any inconvenience I may have caused to the President and members of the Society by unavoidable postponement in the delivery of this lecture. Again, permit me to express the especial honour I feel as a neurologist in following Dr. Hughlings Jackson and Sir William Gowers, who are justly looked upon as founders of English neurology; this makes the task, however, for me all the more difficult.

In selecting a subject, I decided upon the title of "The

* Considerable additional matter has been added, including the examination of the cortex of the Lemur and the convolutional pattern in over 100 human brains.

Visual Cortex," although my lecture is based upon observations and reflections upon the progressive evolution of the structure and functions of the visual cortex in mammalia.

SYNOPSIS.

I. The fundamental principles underlying progressive evolution of structure and function; associative memory and the development of the neo-pallium.

II. The functional and structural evolution of the visual cortex in mammals, its correlation with mode of life, especially mode of feeding.

III. The reciprocal simultaneity in the development of the directive and executive faculties.

Panoramic vision of the lower mammals and association of visual images with kinæsthetic impressions of locomotion for orientation. Binocular vision of the higher mammals, especially of the primates in relation to the development of the tactile kinæsthetic sense and macular vision, finding its highest expression in man, with his erect posture and complete dissociation of the fore limbs from progression.

IV. The progressive development in the primates of the higher association centres. The parietal lobe and its relation to intelligence, the effects of the progressive expansion of the cortex of this lobe on the visual cortex.

The "visuo-sensory" and "visuo-psychic" regions, their delimitation in the primates, the progressive expansion of the latter.

Motor innervation and cortical representation.

V. Clinico-anatomical and experimental data supporting the conclusions.

VI. Some further histological details.

I. THE FUNDAMENTAL PRINCIPLES UNDERLYING PROGRESSIVE EVOLUTION OF STRUCTURE AND FUNCTION.

The fundamental principle underlying the progressive evolution of structure and function in biology is the preservation of the individual and the species—in fact, quest for food, safety by flight, or some other special means,

and reproduction. There is in this progressive evolution, borrowing the expression from Herbert Spencer, a reciprocal simultaneity in the development of the directive and executive faculties. In the lower types of vertebrates some special sense, with its appropriate motor adaptations, predominates, *e.g.*, vision in birds, and smell in the lower mammals. The earliest portion of the cerebral cortex of mammals to appear, both phylogenetically and ontogenetically, is that of which the function is connected with the sense of smell. This cortex is myelinated earlier, and has a different cellular lamination to the rest of the cortex; it is termed archipallium, and is represented in all the mammalia and in some of the lower species, *e.g.*, the insectivora, in which it forms the great bulk of the hemispheres; but as the sense of smell becomes less important in the animal series as a means of preservation of the individual and the species, so it dwindles relatively, and eventually is more or less covered or overlapped by a phylogenetically newer cerebral cortex—neo-pallium—sub-serving the functions of vision, hearing, and tactile kinæsthetic senses, and their associated memory. Even though a large neo-pallium develops, the early predominance of the sense of smell persists in most mammalia, unless an unsuitable mode of life deposes it, as in the cetacea, in which the olfactory cortex is absent.

The distinctive feature of the human cerebral hemispheres is a general cortical expansion especially of the neopallium; not restricted to any particular localised areas, although in some regions expansion is much greater than in others. This increase of the cortex generally, and of certain regions in particular, we may associate with the fact that associative memory is a vastly greater potentiality for the storage and comparison of sensory impressions in man than that of any other animal. The largest ape brain is approximately only half the size of the smallest normal human brain, and the average gorilla's brain is only about one-third the weight of the average human brain. The superficial area of the cortex cerebri in man is more than three times that of the gorilla, and this is due to the increase

in the number and complexity of the sulci and convolutions, and especially to the development of the superficial and deep annectant gyri. This great increase is not so much around the primary fissures, sylvian, central, calcarine (the sensory spheres), as in the frontal, temporal and parietal lobes.

An endeavour will be made to show what part vision, as a directive faculty has played in this great increase of the neo-pallium in mammals from the lowest types up to man. By the kindness of my assistant, Dr. Watson, who is engaged in a research upon the cell lamination in lower types of mammalia, I have been enabled to examine, compare, and have accurate drawings made from photomicrographs according to scale of the visual cortex stained by Nissl method, of the following various orders of mammals.* I am also indebted to him for much valuable assistance in localising the visual area.

II. THE STRUCTURAL AND FUNCTIONAL EVOLUTION OF THE VISUAL CORTEX IN MAMMALS.

(I.) *Insectivora.* (II.) *Rodents.* (III.) *Marsupials.*

- | | | |
|----------------|------------------|---------------------|
| (a) Shrew.* | (a) Guinea-pig. | (a) Wallaby.* |
| (b) Mole.* | (b) Rabbit.* | (b) <i>Dasyura.</i> |
| (c) Hedgehog.* | (c) Chinchilla.* | (c) |

(IV.) *Ungulates.* (V.) *Carnivora.*

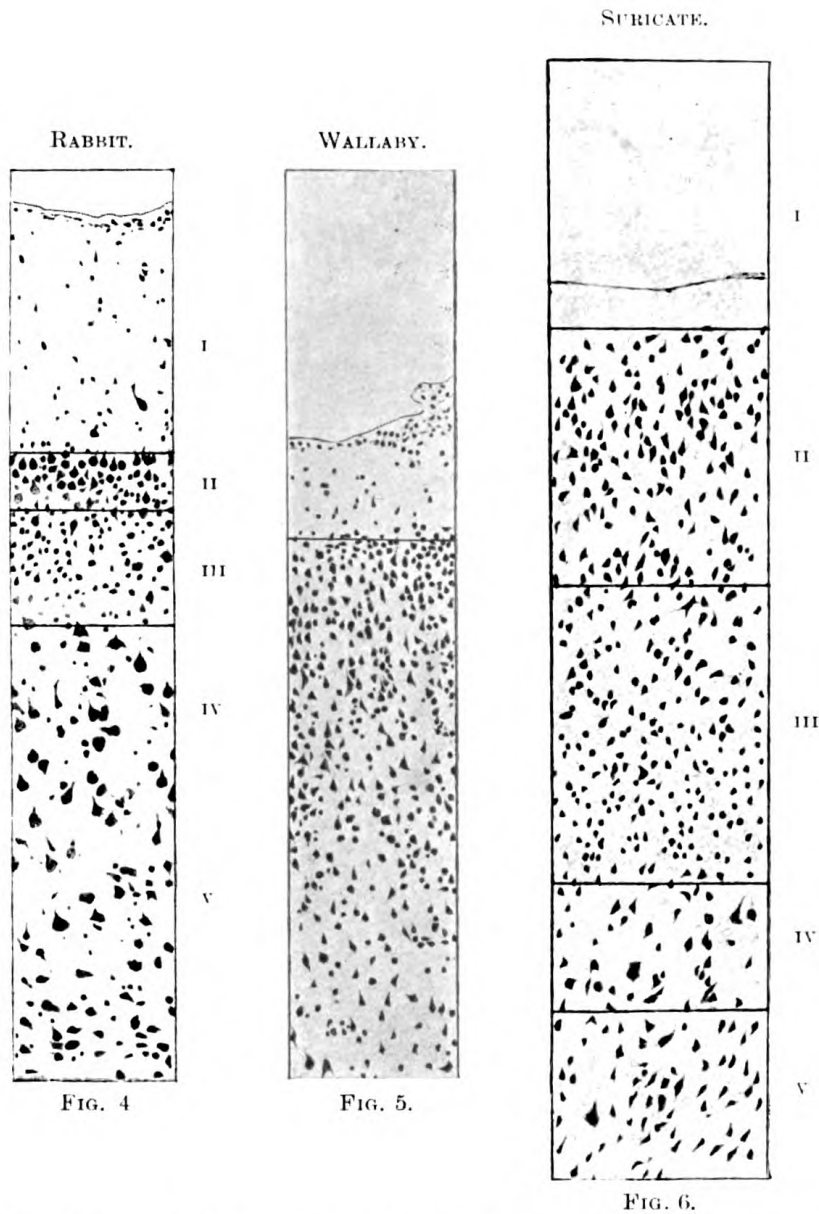
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|----------------|----------------------|
| (a) Muledeer.* | (a) Suricate* |
| | (<i>Viveridæ</i>). |
| (b) Camel.* | (b) Cat. |
| (c) Pig. | (c) Dog. |

(VI.) *Lemuridæ*.¹ (VII.) *Primates.*

- | | |
|-------------------|----------------------------|
| (a) Lemur Mongoz. | (a) <i>Macacus Rhesus.</i> |
| (b) „ Bruneus. | (b) Chimpanzee. |
| (c) „ Catta. | (c) Man. |

* From specimens prepared by Dr. Watson.

¹ Since giving the lecture Miss A. Kelley has received a grant from the Royal Society for the purpose of making a complete histological survey of the lemur's brain under my direction. I am therefore able to include an account of the visual cortex in this animal.



FIGS. 4, 5, 6.—Rabbit, wallaby and suricate. The types of cortical cell lamination of (4) rodent, (5) marsupial, and (6) a small carnivorous cat-like animal belonging to the Viveridae are shown for comparison. These animals are of about the same size; 4 and 5 are vegetable feeding, with panoramic vision; 6 a carnivore, with stereoscopic binocular vision. Observe (ii) the deep supra-granular pyramidal layer and the relatively small (v) polymorph layer, as compared with 4 and 5. In the wallaby it is impossible to make any distinctive limitation of the layers; in the rabbit it is easier. The striking fact, however, is the depth of cells below the granules (iv and v), and the narrowed mixed zone of stellate cells and pyramids above the granules.

Face p. 5—*a*.

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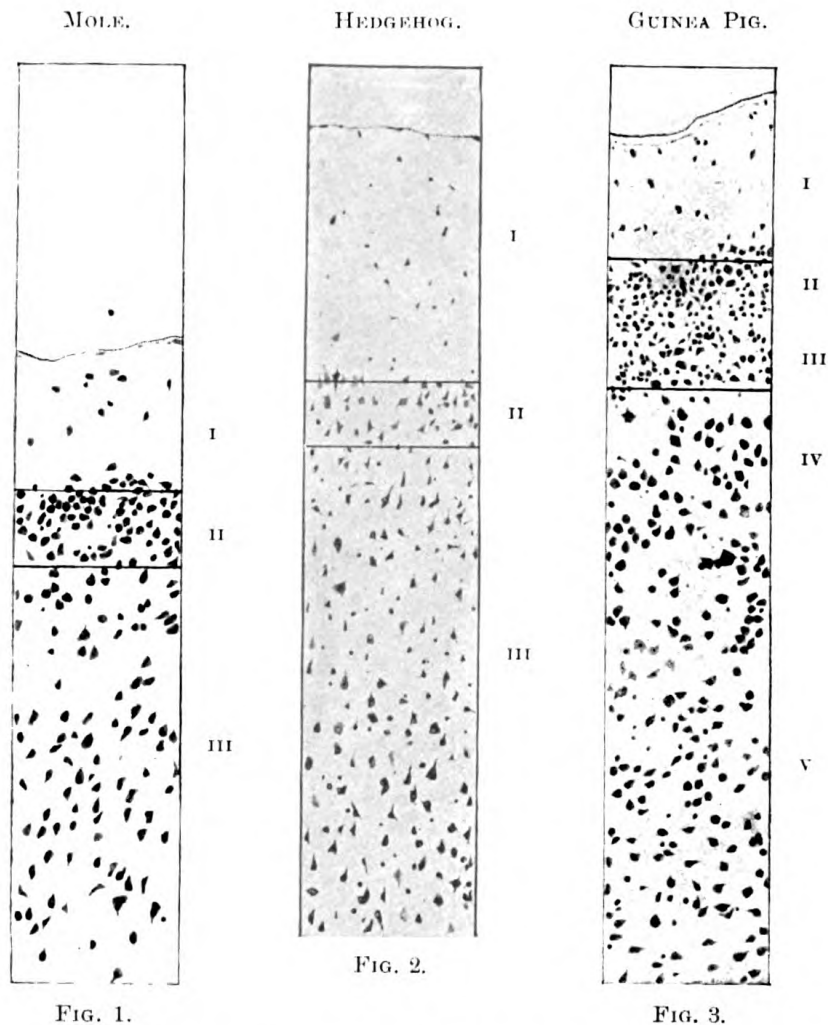
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FIGS. 1, 2, 3.—The mole, hedgehog, and guinea pig. In none of these three animals is vision an important function. The two former are nocturnal insectivora; the type of cortical lamination is very simple as compared with other parts of the neopallium. The cortex of the guinea pig shows a much more definite layer of granules, among which are scattered stellate cells.

Face p. 5—5.

Figs. 1 to 15 inclusive are drawings from photo-micrographs of sections of the visual cortex of mammals 5 μ in thickness, cut in paraffin, stained with polychrome blue, and magnified 120 diameters. As near as possible a similar situation was selected, and in the same plane, as regards cortex and adjacent white matter; but it must be recognised that this is very approximate.

i. Zonal layer. ii. Pyramidal. iii. Granules and stellate cells. iv. Inner-line of Baillarger with large solitary cells of Meynert. v. Polymorph layer.

A glance at figs. 1 to 15, which are faithful reproductions of the specimens drawn to scale with the aid of photomicrographs by Miss A. Kelley, shows a vast difference in the cell structure of these different orders of mammals, and there is no difficulty in seeing this, if we look at the two ends of the series and follow then the structure through the successive types.

GROUP I.—*Vision rudimentary and hardly serving as a directive faculty.*

The mole and the shrew, which are popularly believed to be blind, have the simplest structure—their optic nerves are mere threads, their vision is rudimentary, and probably they are only able to perceive light from darkness. The cell structure of their visual cortex consists almost entirely of small stellate or quadrilateral cells, which look like granules. Below this is a thin layer of polymorph cells, and there are occasional large pyramidal-shaped cells; now these three types of cells are found in all the specimens, but, as will be seen, the relative proportion varies.

In the hedgehog, a nocturnal insectivorous animal, the cells are more complex in structure, but the type of cell lamination is quite simple; the principle directive faculty of this animal being smell (*vide* figs. 1 and 2).

GROUP II.—*Panoramic vision, eyes set laterally, very extensive range, but little elaboration and very elementary association.*

In the rodents examined it will be observed that the visual cortex is more complex than in Group I., and taking

the rabbit, in which vision is a much more important function than in the guinea-pig, we find large stellate cells and branching pyramids closely packed together in a thin layer lying above the granules—these stellate cells, according to Cajal, are the visuo-sensory cells; whether there are a few medium-sized pyramidal cells or not I am not prepared to say. There are certainly very few, and still fewer in the guinea-pig (*vide* figs. 1 to 6).

Stained for fibres, there is a well-marked line of Gennari. You observe a double horizontal layer of fibres in the cortex, the lower being the line of Gennari, which in these animals consists in great part of the terminal plexus of the arborisations of the corticopetal optic radial fibres. Now, in these animals—the rabbit and guinea-pig—the eyes are set laterally, and practically all the optic fibres decussate at the chiasma, and a panoramic or periscopic monocular vision, which is best adapted for its preservation, obtains. It is probable that in panoramic vision the range is extensive, but the perception of depth, of relief, and of solidity are comparatively imperfect.

GROUP III. *Marsupials. Herbivorous; carnivorous.*

The wallaby has a peculiar cell lamination, but I am unable to make any definite statement about it, except that the pyramidal layer is imperfectly represented (*vide* fig. 5). This fact is of interest seeing that it is a herbivorous animal; whereas the *Dasyura*,² which is a cat-like carnivorous marsupial, was found to have a well-defined layer of pyramids above the granules.

GROUP IV. *Ungulates. Vision mostly panoramic and extensive in range, but a variable (according to the setting of the eyes) degree of binocular vision.*

I have examined the visual cortex in the pig, camel, and muledeer: in these animals, as in nearly all the ungulates, the vision is mainly panoramic; there are relatively

² By the kindness of Dr. Albert Wilson I was able to examine a section of the visual cortex of this animal.

few direct fibres in the chiasma. Looking at the drawings of the sections of the visual cortex which occupies an extensive area³ of the posterior surface of the hemisphere, we note a cortex of considerable depth, but this is, in part, due to the relatively large size of the animals, the brains of which have been examined. The cell lamination exhibits relatively a deep polymorph layer, numerous solitary cells of Meynert, a layer of large and small stellate cells; above this cell layer there are a fair number of supra-granular cells corresponding to the pyramidal layer, but this layer is not developed to the same extent proportionally as the other layers (*vide* figs, 7, 8, 11). Examined by fibre method, there is seen to be a well-marked line of Gennari. The pig, which belongs to the ungulates, has a fairly well-developed layer of supra-granular pyramidal cells.

GROUP V. *Carnivora*.

We may divide this group into two sub-groups.

(1) *Caninæ* with eyes set farther apart than the *Felidæ*, so that convergence of the visual axes is not possible, still, there is a considerable amount of binocular, as well as panoramic vision. These animals have an incomplete optic decussation, an extensive area of visual cortex, and, besides the other layers of cortical cells lying below the layer of granules common to the previously-described orders, they have a fair depth of small and medium-sized pyramids (*vide* fig. 10). The line of Gennari is easily displayed by staining for fibres. Canines seize their prey by the teeth, and, in the case of the greyhound or terrier, depend upon a rapid correlation of the visual and motor faculties in hunting and seizing their prey.

(2) *Felidæ*.---The visual cortex of the suricate and the domestic cat have been examined. The former belongs to the *Viveridæ*, and we do not know its habits so well as the latter; probably, in common with all the species, the paw of this animal is an important executive agent in obtaining

³ Mapped out by Campbell in the pig.

food under the direction of vision, though not to the same extent as in the domestic cat, for the claws are only semi-retractile. The paw operating singly under the direction of binocular stereoscopic vision is capable of many and variable refined movements. If we watch a cat play with a mouse we can understand that there are numerous and varied associations between tactile, motor, and visual sensory motor impressions. The correlation of the directive faculty of vision and the executive faculty of the paw is only possible to an animal capable of converging its visual axes, and necessitates, consequently, a suitable setting of the eyes in front of the face, not too far apart, and with the nose not intervening.

A striking feature about the visual cortex of the cat is the depth of the pyramidal layer. The solitary cells of Meynert are numerous, and the polymorph layer relative to the visual cortex of the rodents and ungulates is diminished (*vide* figs. 9, 3 and 4, 7 and 8). It is of interest to note, and in this I am supported by the opinion of an eminent authority, — Professor Sherrington — that the pyramidal tract in the cervical region of the cord representing the volitional path of the executive faculty is probably better developed in the cat than in the dog, and certainly infinitely better developed than in any of the lower orders of mammalia described. We thus see, even at this stage of the animal series, a simultaneity in the progressive development of the anatomical substrata of the visual, directive, and tactile motor executive faculties, as exemplified in the former by the marked development of the pyramidal higher associational layer of the visual cortex. There is in the Felidæ a specialisation of the fore limbs for prehension of their prey which would be less effective for the purpose without stereoscopic vision, and I regard this as the important determining factor in the production of binocular stereoscopic vision, rather than as suggested by Dr. Wilfred Harris in his original and interesting paper on binocular vision in man and other vertebrates, that it is due to nocturnal habits. The cats are probably the first animals in the series of mammals in which section of the optic tract produces

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FIG. 9.—DOG.

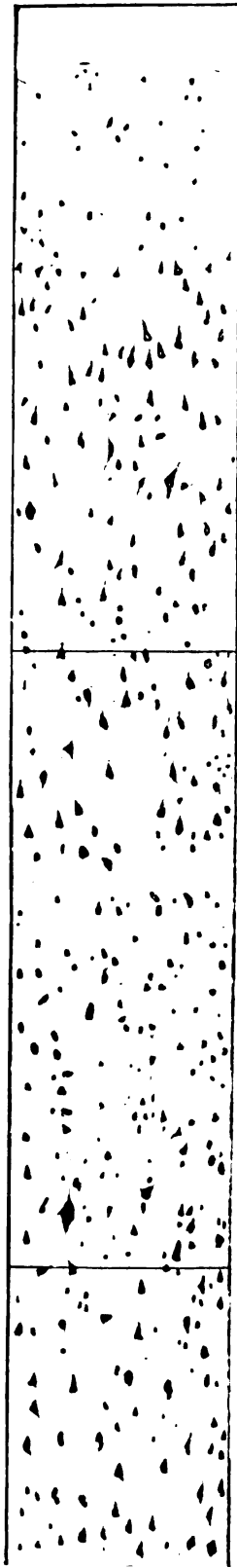


FIG. 10.—CAT.



FIGS. 9 and 10.—Type of cortex of Carnivora, cat and dog. The striking feature is the relatively greater depth of the granular and pyramidal layers as compared with the polymorph layers. There is a suggestion of a double layer of granules. The lines which are drawn across to separate the different layers are only approximately correctly placed.

FIG. 10a.

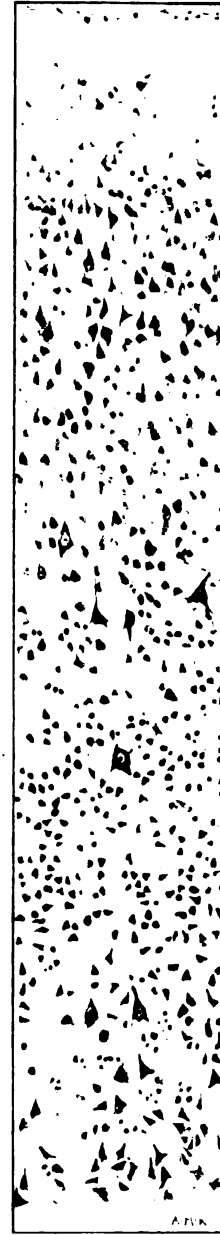


FIG. 10a.—The visual cortex of Lemur Brunensis. The animal was smaller than an average-sized cat; the depth of the cortex is a little less, and the pyramidal layer is not quite so well defined.

FIG. 7. FIG.

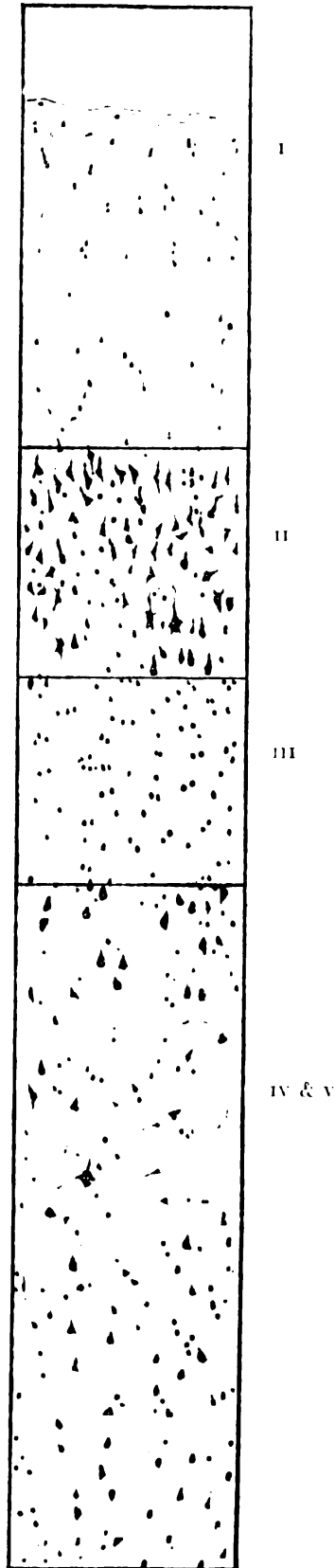
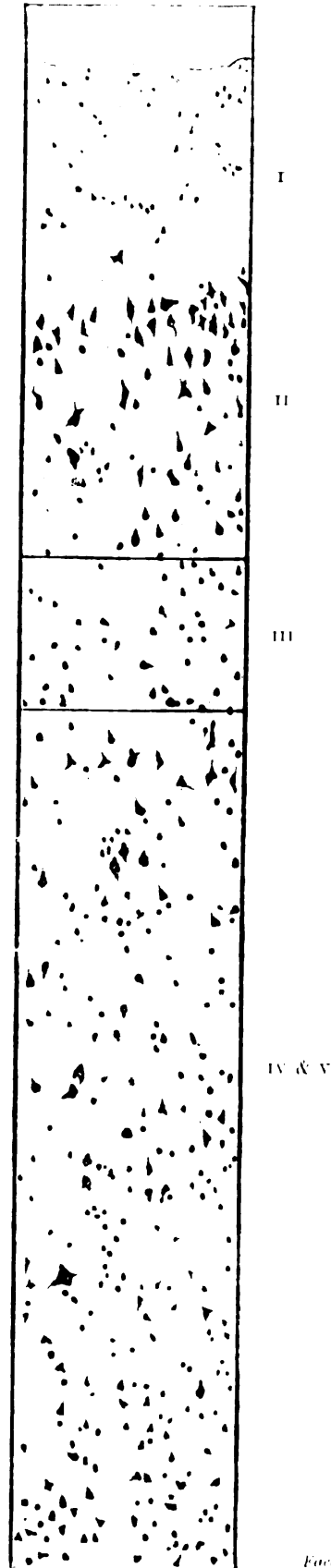


FIG. 8. — CAMEL.



Figs. 7 and 8.—Type of cortex met with in the Uogulutes, pig and camel. It will be observed that layer II, supra-granular, consists of stellate and irregular pyramidal cells; it is a mixed layer of much greater relative depth than in rodents, but considerably less than the carnivora. The infra-granular layers (IV and V) occupy about one half the cortex. It is impossible to fix the line of delimitation of IV and V.

hemianopsy (Harris), and are capable of convergent stereoscopic vision, therefore of eye movements independent of head movements. Animals with panoramic or semi-panoramic vision increase the visual range by movements of the head rather than the eyes. Although the cat, which is capable of convergence of the eyes, probably possesses an area centralis of distinct vision, yet it is not until we reach Group VII., the visual cortex of which we have examined, that we find a macula lutea occurring.

With regard, however, to the existence of a macula lutea, Lindsay Johnson says, "that there is no macula until we arrive at the primates:" but, if by macula we mean a particular specialisation of structure of the retinal elements in the central area of the retina apart from the existence of yellow pigment, then this statement is too sweeping; for Cajal has shown that in the Chameleon there is a central area in which the cones are much more delicate and each separate cone is connected with a separate bipolar cell, and this again with a separate ganglion cell giving off an optic fibre. This specialisation of structure of the directive apparatus of this animal is correlated with a special motor adaptation as Harris has shown, viz., convergence of visual axes, and the darting out of the tongue with unerring exactness to seize its prey. The Chameleon offers then a beautiful example of evolution of a reciprocal simultaneity in the directive and executive neuro-motor mechanisms, but this instinctive neuro-motor mechanism for obtaining live food, so perfect in its way, is only a reflex mechanism incapable of variation as regards judgment of distance, and with very elementary association.

GROUP VI. *Lemuridae*.

The Lemuridae are arboreal animals, nocturnal feeding, with a face like a fox, large ears, very well-developed auditory sense organ, and semi-circular canals, large olfactory nerves and well-developed rhinencephalon. The eyes are set wide apart and convergent vision is not possible. The retina possesses no macula (Lindsay Johnston).

The optic nerves are relatively small, the olfactory

large; there is no occipital lobe, and the cerebellum is always uncovered (Huxley).

The line of Gennari is not visible to the naked eye on section of the brain, but can be seen in sections when suitably stained. There is a faint indication of a sulcus near the pole of the brain on the external surface which marks the limits of the visuo-sensory area. The great part of the striate area is, however, on the mesial surface, as indicated.

The structure of this visuo-sensory area is about equal to that of the cat as regards the supra-granular pyramidal layer (*vide* fig. 10A).

I have observed that these animals do not use their hands in seizing their food when they can take it with their mouth, although they will hold it in their two hands while they eat. Macacus I have found prefers to take food with his hand and carry it to the mouth, and only uses his mouth to seize the food when he is prevented from using his hand.

A fuller description of the brain of Lemuridæ will be undertaken in a later publication, and a correlation of the convolitional pattern and histological structure to the habits and mode of life of the animal, as compared with the Simians, will be given.

Enough has been said to show that the lemurs depend for their preservation upon directive sensory faculties and motor adaptations, thereto different to the Simian quadrumanæ. The sense of smell and its cortical representation of greater phylogenetic antiquity play a much more important part than in the Simians, where its functions have been largely replaced by vision *in association* with the tactile kinæsthetic sense, and a new stereognostic sense developed which finds an anatomical basis in a new cortex. Compare the brain of the Lemur with that of the Ape.

GROUP VII. *Primates*. (a) *Apes*. (b) *Anthropoid apes*.
(c) *Man*.

In this group the eyes are set in front and close together, there is semi-decussation of the optic fibres, and perfect

EVOLUTION OF THE VISUAL CORTX IN MAMMALIA 11

Diagram from a photograph of the mesial and external surfaces of the right central hemisphere of macacus. The figures mark the blocks which were taken out and embedded in paraffin. Sections of 5μ were out, stained with polychrome blue, and the visuo-sensory area delimited by observing the distribution of the double layer of granules with pale stripe (line of Gennari intervening). Each section was drawn as represented in figs. 17 c—17 x. Then the regions of the occipital lobe were correspondingly dotted in the diagram so as to show accurately the exact distribution of the visuo-sensory striate cortex.

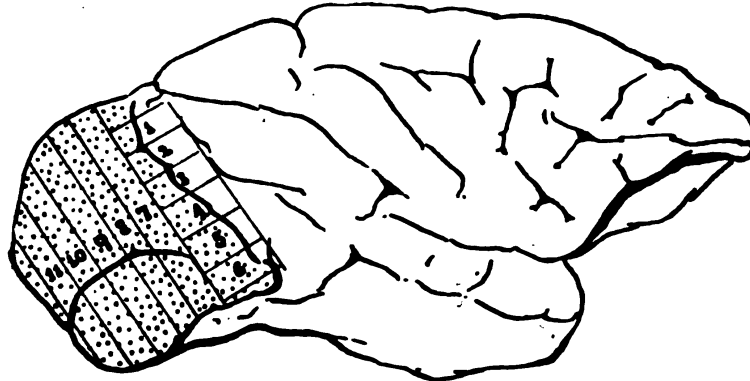


FIG. 17a.

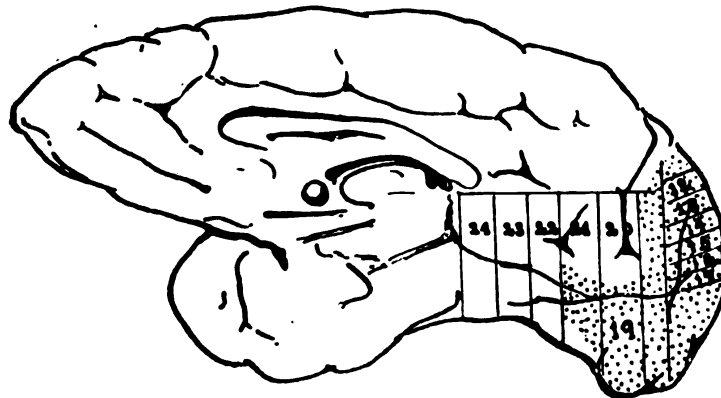


FIG. 17b.



FIG. 17c.

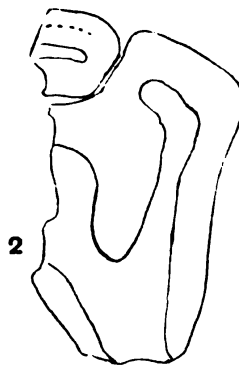


FIG. 17d

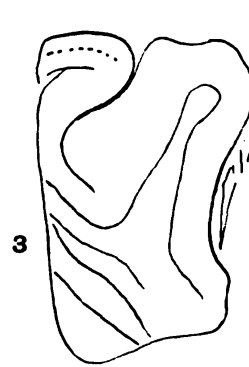


FIG. 17e.

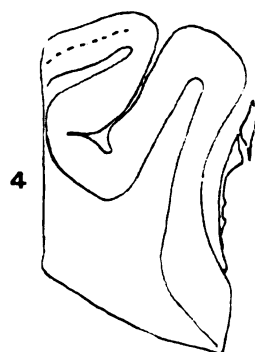


FIG. 17f.

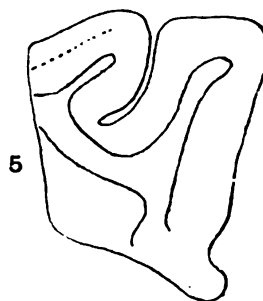


FIG. 17g.

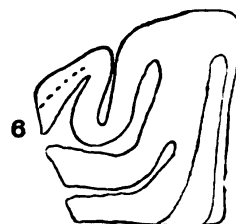


FIG. 17h.

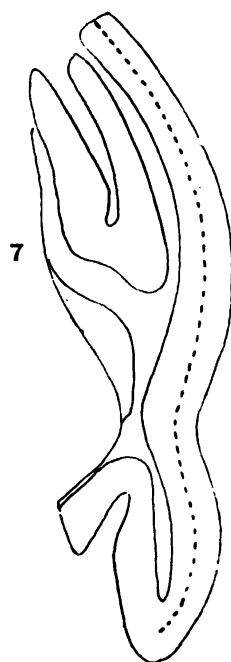


FIG. 17i.

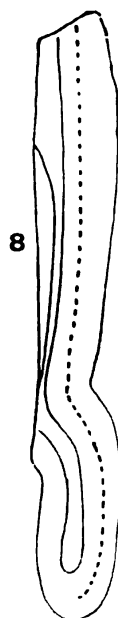


FIG. 17j.

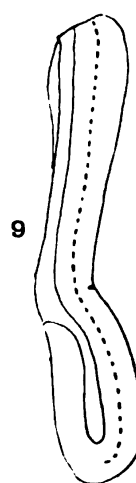


FIG. 17k.

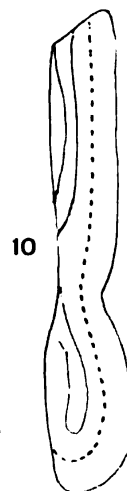


FIG. 17l.

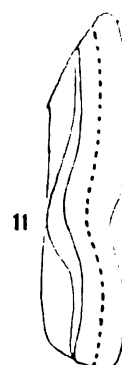


FIG. 17m.

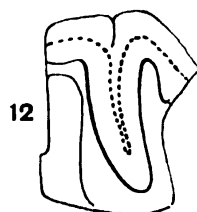


FIG. 17n.

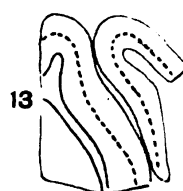


FIG. 17o.

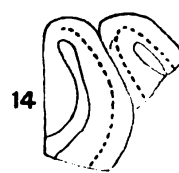


FIG. 17p.

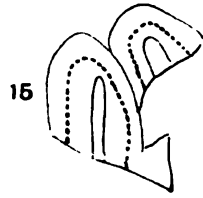


FIG. 17q.

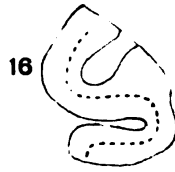


FIG. 17r.



FIG. 17s.

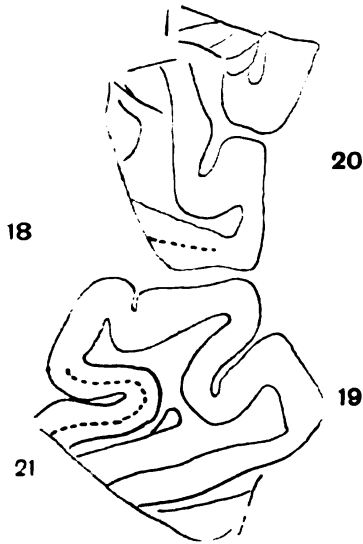


FIG. 17t.

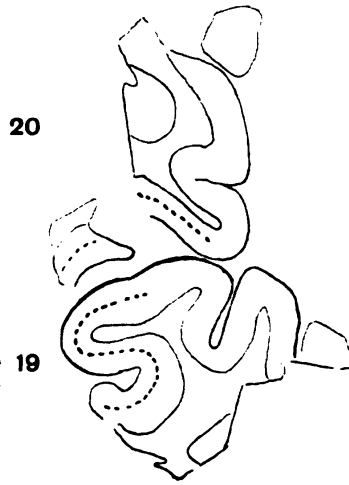


FIG. 17u.

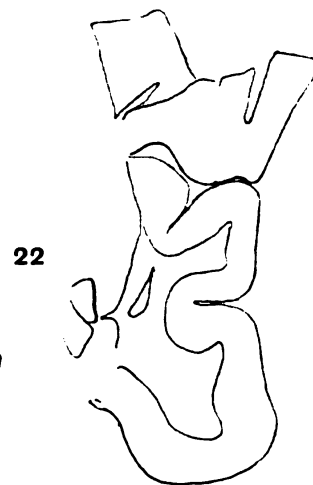


FIG. 17v.

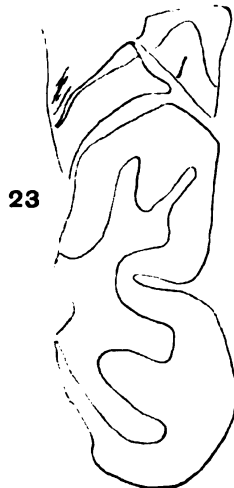


FIG. 17w.

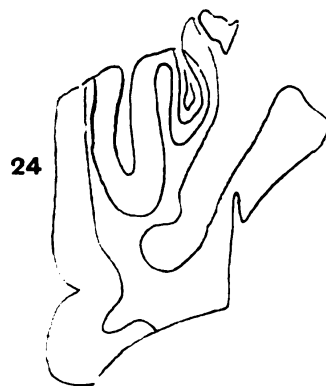


FIG. 17x.

binocular stereoscopic vision, with only a remnant of monocular panoramic vision on the temporal side remaining. The range of vision can be increased by lateral and up-and-down movements of the eyes *independent of* or *associated with* movements of the head and neck. This specialisation of the visual directive functions is coincident with the existence of a definite occipital lobe, and sections of its fresh cortex show a line of Gennari visible to the naked eye. The extent and distribution of the striata area in the occipital lobe of *Macacus* has been mapped out by serial sections mounted and stained (*vide* fig. 17, *a—x*). Microscopic examination reveals a specialisation of structure of the visual cortex, which is as marked in the ape (*Macacus*) as in man. A glance at figs. 12 and 13 will show that there is a double layer of granules (faintly indicated in the carnivora), and above the outer layer of these cells is a deep layer of small and medium-sized pyramids. The structure is quite similar in this visuo-sensory motor area in the ape and man, if we agree with Henschen that the *area striata*, or that part of the cortex which possesses a line of Gennari, is the primary visual cortex or visuo-sensory region of Bolton (*vide* figs. 14 and 15). Circumjacent to this region, and occupying the remainder of the occipital lobe in the primates, is a zone of cortex which commences at the termination of the line of Gennari, termed by Bolton visuo-psychic, and delimited by Campbell in the anthropoid apes and man; it is characterised by the disappearance of the lower layer of large and small stellate cells and the appearance of a third layer of large pyramids. This is shown in the photo-micrograph of a section of the junction of the visuo-sensory and visuo-psychic cortex in the foetal brain, which exhibits this pushing down by the pyramidal layer of the upper layer of granules coincident with the disappearance of the line of Gennari and the lower layer of granules (*vide* fig. 16). As the visuo-sensory cortex closely corresponds with the primordial visual area of Flechsig, so the visuo-psychic closely corresponds with his intermediate area. Now Flechsig has shown by the myelination method that this intermediate associational area is ontogenetically and

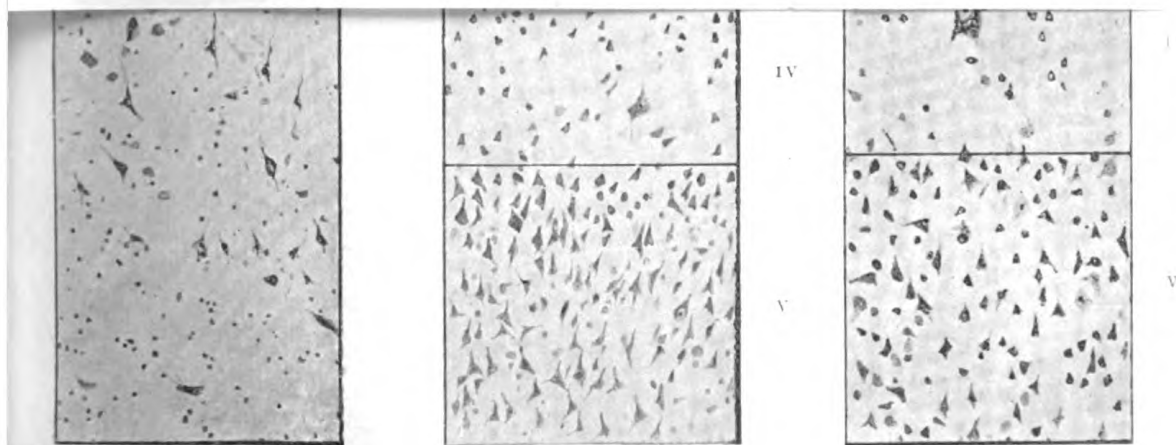


FIG. 11.

FIG. 12.

FIG. 13.

FIGS. 11, 12, 13. — To show the comparison of the type of cortex of a large ungulate (mule deer) with a primate (*Macacus rhesus*, Fig. 12).

FIG. 11. — Mule deer. Compare the number, forms, and depth of the cells of the supra-granular layer of the cortex of this large animal with Fig. 12. There is a single layer of granules and a deep infra-granular which cannot be delimited into two definite layers (IV and V); the depth, however, of this layer is relatively twice that of the ape.

FIGS. 12 and 13 show the comparative cell lamination of the visuo-sensory (Fig. 12) and the visuo-psychic (Fig. 13) cortex in the ape. The layers correspond to those found in the human, described in Figs. 14 and 15.

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phylogenetically of later development than the primordial visuo-sensory area; moreover, it is but little developed in animals below the primates, but becomes a definite area in apes, still more definite in anthropoid apes, and in man

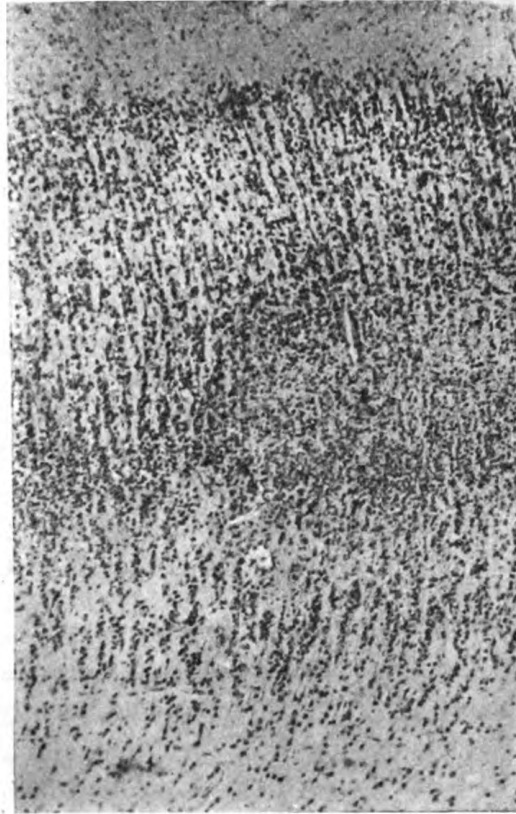


FIG. 16.

Section of brain, 7 months to 8 months fetus, at the junction of the visuo-sensory, and visuo-psychic regions, showing the double layer of granules with intervening line of Gennari replaced by a single layer of granules, on an increased corresponding depth of the pyramidal layer. The large pyramids are distinctly seen in the lowest level of the pyramidal layer. Beneath the inner layer of granules is a pale line corresponding to the inner line of Baillarger, and beneath this is the polymorph layer of cells.

most extensive of all. As Dr. Campbell's excellent work shows, it covers the occipital lobe with the exception of the calcarine region. Contrasting, then, the microscopic structure of the visual cortex of the primates with the

lower mammals, we find that the main differences are the existence of an occipital *lobe*, the cortex of which consists of two structurally-different regions: (1) Visuo-sensory, which attains its maximum extent and complexity of cell and fibre structure in the ape, characterised by an increase of the width of the line of Gennari, a double layer of granules, and above the outer a deep layer of small and medium-sized pyramids; (2) Visuo-psychic or associational, either not definite or as a very narrow zone in animals below the apes, and characterised by an increased depth of the pyramidal layer, owing to the presence of a third layer of large associational pyramids. This associational zone increases in area with the progressive evolution of the primates, and occupies a large part of the superficies of the occipital lobes in the highest types of human beings.

My observations on the visual cortex of mammals thus tend to show a parallelism between the progressive development of the pyramidal layer in the visual cortex of mammals and the progressive development of binocular vision. The cells of this pyramidal layer, as figs. 9 to 15 show, are small, medium, and large sized; they are association neurons phylogenetically of later development. They are also, as Bolton has shown, of later development ontogenetically, for whereas the polymorph layer has attained about its full depth at birth, the pyramidal layer is not more than one-half its proper depth.

Dr. Watson is of opinion, from a careful study of cortical cell lamination in different orders of animals, that the deep polymorph layer of cells which is present in all is concerned with lower associative memory, while the later developed pyramidal layer is concerned with higher associative memory and educability.

It is, therefore, probable that this more superficial supra-granular layer of pyramidal cells does not function till some time after birth; for Flechsig has shown that fibres of the optic radiations are only myelinated at birth as far as their first bifurcation, and are demonstrable as myelinated fibres only as far as the second lowest layer of the cortex. Since myelination indicates preparedness for function, the

seat of primary cortical visual activity (that is the region concerned especially with perception of various degrees of intensity of luminosity and darkness) is situated in these lowest layers which we have observed are present in all, even the lowest mammals. In support of this statement it may be remarked that the horizontal fibres of the cerebral cortex, especially of the line of Gennari, are still completely non-myelinated at birth.

Flechsig distinguishes three sets of fibres in the primary optic radiations—sensory, myelinated at birth; motor, at birth or soon after; and associational, in which the myelination, however, occurs pretty late. Now Cajal, from histological observations, concludes that the line of Gennari is formed by the last ramification of the optic fibres, and he calls it the optic plexus, or the stripe of Gennari. The optic fibres form in the fourth and sixth layers a thick feltwork of fibres, in the meshes of which are situated the stellate cells. Cajal says it is necessary therefore to consider these layers as the principal place in the grey substance, in which is projected the optic image, and where the optic sensation takes place. The atrophic changes in the visual cortex as a result of longstanding blindness or anophthalmos recorded by Henschen, Monakow, Cramer, Leonowa, Bolton, and others are not in accord. Henschen states “from the description of the observations cited it results then, that one is not authorised in drawing any conclusions on the subject of the layer of the cortex which is in most direct relation with optic conduction,” although if there is any balance of opinion it is in favour of the deeper layers being most affected. As to the ribbon of Gennari one can only conclude that it participates to a certain degree in cortical atrophy.” We must, therefore, assume that there are some fibres at any rate in the ribbon of Gennari in the primates which are not derived from the neurons of the external geniculate body. This conclusion is supported by the fact that Bolton found in his case of anophthalmos one half of the fibres still remaining in the line of Gennari. Now we have observed that this stripe in the grey matter of the cortex becomes distinctly visible to

the naked eye first in the primates when the pyramidal association system is fully developed, and that this is coincident with a macula, and with perfect binocular vision. It is therefore a legitimate inference to suppose that the felt-work of fine fibres forming the line of Gennari is partly made up of association fibres of the optic radiations coming by way of the splenium from the opposite occipital lobe. This view will explain why there should be a double layer of granules in the primates, the upper layer belonging to the associational pyramids and forming the intercalary neurons. It would, moreover, tend to show that it is the upper layer of granules which is continuous with the single layer found in the visuo-psychic region (*vide* figs. 14, 15, 16).

III. THE RECIPROCAL SIMULTANEITY IN THE DEVELOPMENT OF THE VISUAL DIRECTIVE AND TACTILE MOTOR EXECUTIVE FACULTIES.

Rochon - Duvigneaud gives an admirable summary of Cajal's work upon the different modes of association of the two eyes for vision, panoramic vision, and the total decussation of the optic nerves, the progressive fusion of the visual fields in the higher mammals, and the correlated development of the direct bundle.

In panoramic vision of the lower mammals with their eyes set laterally, the total visual field formed by the juxtaposed two monocular fields is very extensive and very acute, and their power of orientation is good by virtue of the association of visual images with the kinæsthetic impressions of locomotion; but it is highly probable that the sensation of relief and of depth is rudimentary because the visuo-kinæsthetic associations are with smell, hearing, and locomotion, and not with complex, varied, and refined tactile-motor impressions. The motor associations are elemental and are mainly concerned with orientation.

Animals with power of convergence of the visual axes have a common visual field, and vision gains in quality, notably by the perception of relief, while it loses in range.

The two retinae, in place of receiving each image, having no point in common between them, receive on the contrary the same images in their whole extent. When the visual fields coincide, the amount of binocular vision increases in the zoological series from the rabbit to man. But simultaneously, as Edinger remarks, one sees a direct bundle develop and progressively increase in the number of its fibres in the same series so that we can correlate these facts with the progressive development of the pyramidal layer of associational cells, which I have pointed out as occurring in the series of mammals. The relation between the direct bundle and binocular vision already understood by Newton, is very easy to comprehend if one refers to the scheme of Cajal. When the two eyes are directed forward and fix the same object (the arrow) it necessarily results that the homonymous halves of the two retinae (that is the two right halves or the two left halves) receive respectively the image of the same half of the objects. It is necessary in order that there should be no diplopia that these two similar images be transported to the same point of the brain, where they will undergo fusion.

"How the function has been created, what intimate mechanism and modification in the convergence of the ocular axes has determined the formation of a direct bundle we are still far from knowing, in spite of Darwinian explanations on this subject" (Rochon-Duvigneaud). But we have seen that correlation in the progressive development of the visual directive and the motor executive faculties is a truism based on the Darwinian principle of adaptation to environment, and modifications of structure and function for the preservation of the individual and the species, especially as regards the feeding habits of the animal, as Harris has so admirably demonstrated. Thus animals which prey upon other animals must possess special powers of motor adaptation guided by vision. Prof. Sherrington informs me that his observations on binocular flicker taught him that the convergence of the fibres of the right half of right retina and right half of left retina in the highest mammals towards the same, *e.g.*, right occipital lobe, is probably

because they both have to initiate the same movements of eyeballs and hand—that is to bring both paths to the same foci of executive administration of motor apparatus, *e.g.*, eyeballs and head and neck and hand. He does not agree with the simple explanation that Cajal gives in his

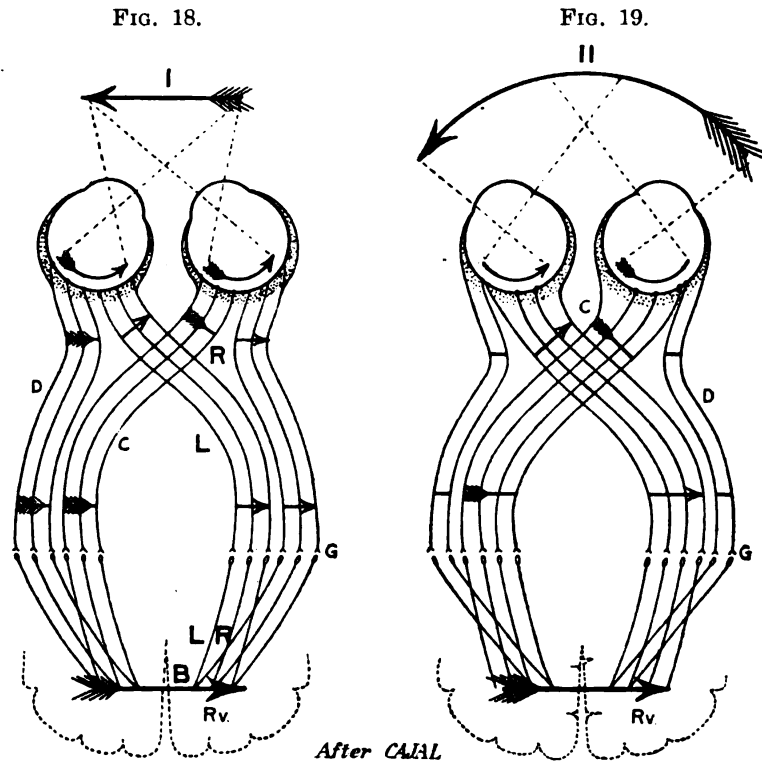


FIG. 18.—Schema (after Cajal) to show the formation of the mental image by synthesis of visual representation, transmitted by the two optic nerves in man and mammalia having a common visual field in both eyes; (*d*) homolateral optic bundle, crossed bundle; (*ex*) external geniculate body; (*Rv*) cortical visual centre and reconstitution of the mental image.¹

FIG. 19.—Schema of the chiasma, of the optic tracts, and of the optic projection in the brain of a mammal, with semi-panoramic vision; (*c*) crossed optic bundle; (*d*) homolateral optic bundle; (*G*) primary optic centres; (*Rv*) visual cortical centre, with mental projection of the object.

diagram of the fusion of similar points of the image from homonymous halves of the retina at identical points in the occipital lobe; his valuable experiments on binocular flicker entirely controvert this. For if the point B in the diagram (fig. 18), viz., the place of meeting of L L and R R, feels the

tremor of the flicker conveyed by LL, how can it go on feeling that tremor when it is conjointly receiving an exactly inverse tremor from RR, which exactly fills up with light the shadow intervals belonging to LL? Or how is it on the same plan that the tremor received by B from LL is not accentuated upon the successive light and shadow intervals of RR when they are timed so as to exactly agree and coincide with those from LL? Again, on Cajal's and similar plans, how is it when corresponding areas of the two retinæ are stimulated by one and the same luminous object, so that the stimulation of R gives a monocular visual image say of brightness = 10, and therefore also a visual luminosity at the other retina of 10, the visual luminosity of the combination (binocular) of the two $R + L$ is not according to Weber's law, nor any simple summation, but is simply 10 still? Again take binocular colour mixture; in it two complementary colours, red and green, do not make grey, but an oscillating sheeny surface, varying from red to green and back again (retinal rivalry).

Although these experiments clearly show there is not fusion in the simple manner indicated by Cajal, yet the following experiments proved that perceptual fusion does occur:—

(1) The unlike contour of component uniocular images passing to the resultant binocular contour intermediate between its components.

(2) The right eye seeing an after image when the left only has been offered a visual image.

(3) Damping of flicker in one by a *steady* image at the twin area of the other (Sherrington).

(4) The appearance of contrast colour in a grey image at right eye when a coloured otherwise similar image is offered to the other.

It is probable that this more complex elaboration of the visual sensations accompanying binocular stereoscopic vision is phylogenetically and ontogenetically of later origin, and it is not an unwarrantable inference that this sheet of associational cells (which we have observed is ontogenetically and phylogenetically of later development) plays

FIGS. 20—25.—Photographs of the occipital lobe looked at from the pole of—

Fig. 20. Macacus, showing the smooth surface bounded in front by the *affenspalte*.

Fig. 21. Chimpanzee, showing the visuo-sensory area has been infolded by the development of an increase of temporo-occipital annectants, but also, though to a less degree, by occipito-parietal annectants. The visuo-sensory area is triangular, with the narrow portion of the triangle forwards. A large portion of the striate cortex lies in the deep fissure running backwards to the pole.

Fig. 22. Right occipital lobe of a human subject, in which there was imperfect parietal development. The situation of the pole is shown by a *. The posterior part of the retro-calcarine fissure is seen to extend a considerable distance beyond the pole to the external surface.

Fig. 23. Shows the retro-calcarine fissure terminating on the mesial surface within the pole.

Fig. 24. Lateral aspect of left occipital region of a Fellaheen. Brain showing line of section (*d*) and (*a*) sulcus lunatus, (*b*) accessory intra-striate, and (*c*) intra-striate ; (*e*) infra-striate sulcus.

Fig. 25. The appearance of surface of the section, showing (*a*) calcarine fissure ; (*b*) accessory intra-striate sulcus ; (*c*) end of line of Gennari at a point midway between *b* and *a*, sulcus lunatus. From photographs kindly supplied to me by Professor Elliot Smith.

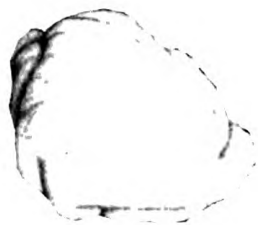


FIG. 20.



FIG. 21.



FIG. 22.

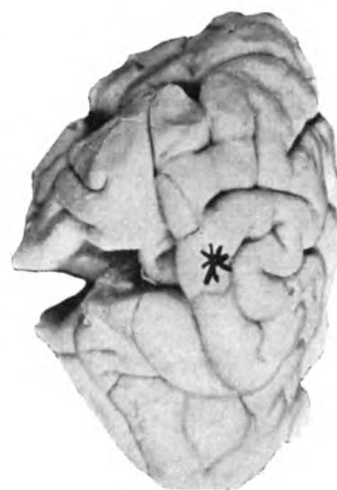


FIG. 23.

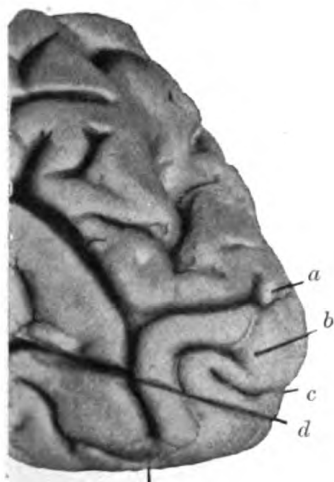


FIG. 24.

Face p. 22.



FIG. 25.



an important part in this elaboration. In view of the important observations of Sherrington the above appears to be much more probable than the untenable hypothesis of Cajal of groups of isodynamic cells in the cortex in which isodynamic groups of fibres starting from corresponding points of the retina end. Another important point in binocular vision is the fact that for the convergence of the visual axes innervation currents must flow from both occipital or frontal lobes. Schäfer and I, also Munk and Obreggia, found that stimulation of the frontal or occipital cortex gave rise to lateral deviation when excited, but when identical points, which previously excited simply gave rise to lateral deviation, were stimulated with equal currents, the axes previously slightly divergent became parallel, and very frequently underwent convergence. The sensory impressions coming from the structures moved are associated with the visual images. Again, the conjugate movements of the head and eyes in following a moving object give rise to kinæsthetic sensory impressions, which fusing with macular visual impressions produce in consciousness a series of impressions by which judgment is formed of the rate of movement of the object. This function is later acquired, for the observations of Preyer on the infant, and Steiner¹ on animals

¹ Steiner did not make any experiments upon primates, but he points out that the development of vision occurs in two periods in the infant. At the fifth week it is able to see an object held in front of it, but like the dog at the thirty-fourth day, it is unable to follow and fix an object the image of which is projected laterally on the retina. This capacity does not come until the fifth month in the infant, when it may be inferred that the necessary association has occurred. Steiner performed a series of interesting experiments upon young animals at various intervals of days after birth. He showed that the motor cortex responds to excitation before the visual cortex. The guinea pig, born with its eyes open, and set laterally, does not make much use of its panoramic vision and its visual cortex practically possesses no supra-granular pyramidal cells. The motor cortex responded to excitation at birth, whereas stimulation of the visual cortex did not produce a result until the fifth day. In the rabbit the motor cortex was excitable on the ninth or tenth day, the visual not until the fourteenth. Moreover, not until the fifteenth day does this animal make any attempt at flight when one attempts to catch it. The dog is much later; even twenty-six days may elapse before the motor sphere is excitable, although its eyes are open on the fourteenth. It is only at the thirty-fourth day that a dog can avoid obstacles, and seems only to be able to follow his master by the

show that these associated movements of the head and eyes in the higher mammals do not take place till some time after birth. Again, no true ideas of distance, form, extension, solidity and qualities of bodies generally would be conveyed to the mind unless they could be explored by the executive locomotive and tactile faculties. Visual images alone would not convey to the mind the reality of the external world were they not associated with locomotion and previous tactile and kinæsthetic images of manipulation, and it is not too much to say that tactile impressions are those into which most visual impressions have to be translated before their meanings can be known. Thus the hand under the guidance of vision becomes the instrument of the mind. And every visual perception becomes a complexus produced by an action on the retinæ propagated to the visual cortex, and a reaction of the whole brain based on the associative memory of past experiences. Macular vision especially gives rise to a full mental contribution to the perception, by the fact that it involves fixation and attention.

sound of his voice. He certainly sees, for if you present to him a piece of meat directly in front of his eyes he snaps at it. But if the image of the object is projected laterally upon the visual field, the dog does not seek to follow it by an appropriate associated movement of the head and eyes. His visual sensori-motor apparatus is not yet completely developed. At this period the dog's visual cortex is still inexcitable, and it is not until the fortieth day when a dog can follow a moving object that the visual cortex is excitable. The experimental researches of Stirling on the dog's brain show in the area which upon excitation produces movements of the neck a region exists which on stimulation, can produce movements of the eyes independent of the neck movements. There are independent conjugate movements of both eyeballs along from the side stimulated.

Visual sensation is only possible at birth when elemental consciousness obtains, owing to the association systems being still undeveloped. The striate area, which we have reason to believe is the primary seat of vision, the part of the cortex in which the optic radiations terminate, does not occupy the whole surface of the occipital lobe in the anthropoid apes or man. It is limited in man, and to a less degree in the anthropoid ape, to the mesial surface, and that portion of the mesial surface which forms the lips, floor and walls of the calcarine fissure. The superficial extent, however, of the striate area is not relatively less, in proportion to the area of the retina, in the anthropoid apes and man, as compared with the lower apes. A glance at fig. 20 shows that the external surface of the occipital lobe of the ape is smooth, and there is only an indication of a fissure. There is an annectant gyrus between the occipital and temporal lobes, but the lip of the occipital lobe overlaps the parietal, so that the connection between the two is hidden by what may be termed the occipital operculum.

IV. THE PROGRESSIVE DEVELOPMENT IN THE PRIMATES
OF THE HIGHER ASSOCIATION CENTRES; THE EFFECTS
ON THE VISUAL CORTEX.

Now it can be readily seen that if the parietal lobe and its occipital annectants increase at a rate phylogenetically more rapidly than the occipital itself it would tend to push back and infold the smooth striate surface of the occipital lobe of the lower apes, and thus we see that the striate area, which is on the surface of the lobe, becomes diminished, and a zone of phylogenetically new cortex progressively increases in area.

These inferences are supported by the following facts, which will be made more easy of comprehension by the accompanying diagrams (figs. 26 and 27) :

The area which is dotted is the portion of cortex visuo-sensory in function, corresponding to the half-vision centre, and, histologically, is characterised by the presence of the line of Gennari. The shaded area corresponds to the visuo-psychic region delimited by Campbell, characterised histologically by a deep layer of large pyramids and coarse fibres.

Fig. 26A represents the occipital lobe of *Macacus rhesus*, and it will be observed that (as figs. 17a—x demonstrate) the visuo-sensory region occupies the whole of the external surface of the occipital lobe up to the *affenspalte* except the temporo-occipital annectant. It forms an operculum lying over the visuo-psychic cortex, but as this latter and the parietal lobe develop, the striate visuo-sensory cortex is lifted up, pushed back, and infolded so that in the anthropoid apes as shown in B (*chimpanzee*) a wider visuo-psychic zone is apparent, and the *affenspalte*, by the development of occipito-parietal annectants, has become lunate in form. There may be considerable modifications of the extent of visuo-sensory cortex on the external surface of the occipital lobe in the anthropoid apes (*vide* fig. 21) owing to the variability of the amount of development of the before-mentioned annectants. Fig. c represents the distribution of the visuo-sensory and visuo-psychic cortex found frequently in the left hemisphere, occasionally in both and rarely in the right alone.

This figure is taken from the brain of a Congo negro ; the line of Gennari ended at the top of the lip of the anterior wall of the fissure which separates the dotted and shaded areas, so that the full extent of the striate cortex

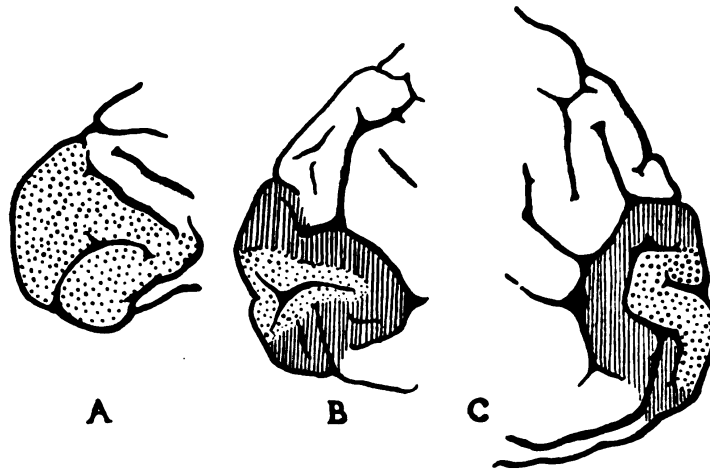


FIG. 26.

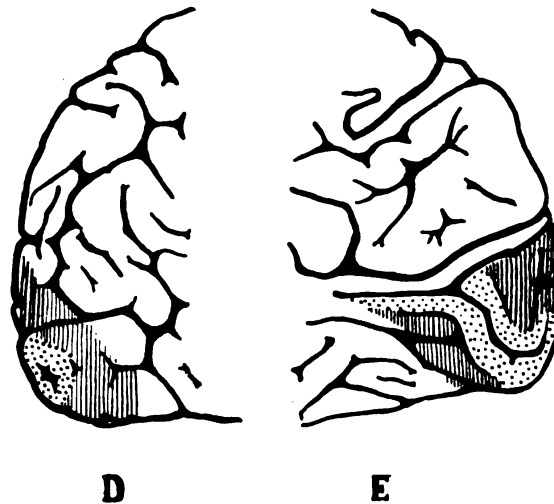


FIG 27.

on the external surface is considerably greater than it appears. In fact, as fig. 25 shows, the striate area ends midway between the intra-striate and lunate sulci.

Fig. 27 D, E shows the distribution of the visuo-sensory

and visuo-psychic cortex in the human brain (after Campbell); it will be observed that in D the striate area is represented as extending a little round the pole. This distribution Bolton and Campbell looked upon as an extreme case. Usually it ends at the pole or on the mesial surface of the occipital lobe, and all the striate area is situated around the calcarine and retro-calcarine fissure, which latter terminates at the pole or on the mesial surface. When it comes on to the external surface, as in fig. 26 c, the striate area follows it; E shows the distribution of the striate area. Anteriorly it is found (as Bolton first showed) only on the lower lip, and it extends, I have found, a variable distance forward. This is the true calcarine fissure found in all mammals, a primary fissure occurring at a very early stage of development. Behind this the dotted striate area is found on the upper and lower lips of the retro-calcarine fissure. The true extent of the striate area can only be determined by opening up the fissure, when two deep-seated anterior and posterior cuneo-lingual annectants will be found; and sections will show that the grey matter of the whole of the floor of the fissure exhibits on section a line of Gennari. If, as is most probable, the striate area represents a cortical retina, the superficial area of it is the same in all human beings; consequently, when the striate area extends well on to the external surface, as in fig. 26 c, the fissure should be shallower, and the deep cuneo-lingual annectants should be superficial. This is what actually happens, the posterior cuneo-lingual annectant especially being found superficial.

Putting all the facts together we observe that the primary visuo-sensory cortex represented by the dotted area always occupies the same superficies, but the placement of it depends upon its relative degree of displacement by cortex of later evolutionary development and functional acquirement.¹

¹ Elliot Smith has renounced his opinion that the left half of the field of vision must be smaller than the right in those persons whose striate area extended on to the external surface of the occipital lobe. Such a view was entirely unphysiological, and in a letter I pointed this out to him. In his

Bolton showed, by his valuable researches on the histology of the visual cortex, that the striate area suddenly ceases owing to the fact that the line of Gennari disappears abruptly, and, coincident with this, the double layer of granules becomes a single layer, and a layer of large pyramids makes its appearance. So that there are now three layers of pyramids instead of two. This region was termed by Bolton visuo-psychic. It has been carefully mapped out by Dr. Campbell in his valuable research on the histology of the cerebral cortex. He has kindly sent me a diagram which indicates the limits of this histologically definite localised area. It corresponds, as you will observe, with the remainder of the occipital lobe. He has shown by his method, as Flechsig had previously shown by the myelination method, that every primordial sensory sphere is surrounded by a zone which may be termed intermedial. The primary sensory motor spheres are situated around the primary fissures, central, sylvian and calcarine. Around these are areas which are myelinated later, characterised by large pyramidal cells and large fibres. There is, as we rise in the zoological scale, a progressive increase of these zones, but in man the great increase of the area of the cerebral cortex, especially in the parietal, temporal and frontal lobes, is due, even in greater measure, to the development of a cortex which is latest myelinated—the terminal areas of Flechsig, in which fine fibres, according to Campbell, alone are found, and in which there is an absence of large pyramidal cells.

According to Flechsig,¹ it is only in the primordial areas that projection fibres are found. This, however, is strongly

reply he stated that before receiving my letter he had shown that each striate area was of the same superficial extent, viz., 3000 square millimetres. It is, therefore, certain that the size of the primary visual area of the two hemispheres is the same, and that the extension of the striate area on to the external surface of the left occipital lobe does not denote an increase of area, but is due to a difference in the growth and development of the remaining structures of the brain and the enclosing structures, membranes, skull, and blood sinuses.

¹ The views of Flechsig are, I may remark, really the same as those put forward many years ago by Sir William Broadbent, who came to somewhat similar conclusions from anatomical and clinical observations.

disputed by such eminent authorities as von Monakow and Dejerine.

We may now inquire what are the causes which have led to this remarkable cortical development in the anthropoids, and more especially in man. It has long been considered that a large frontal development indicates a high order of intelligence, and that is one of the striking features in the difference between the anthropoid brain and that of man. But it will be observed that there is a much greater development in the parietal lobes. "The great size of the parietal lobe is a leading human character, and it has partly gained its predominance by pushing backwards so as to encroach, to some extent, upon the territory which formerly belonged to the occipital lobe."—Cunningham.

Rudinger, who studied the brains of quite a number of distinguished men, including Bischoff, Döllinger, Tiedemann, and Liebig, asserted that the higher the mental endowment of an individual the greater is the relative extent of the upper part of the parietal lobe. Other observers, however, have fixed upon the lower part of the parietal lobe as that in which there is a correlation between a high order of intelligence and a relative increase of surface. Thus, Retzius has stated that such was the case in the brains of the astronomer, Hugo Gylden, and the mathematician, Sophie Kowalevsky. Hansemann described a similar condition in the brain of Helmholtz. Moreover the wide parietal development of the cranium in the skull, of Beethoven, Sebastian Bach, and of Kant, indicate that an increased size of the parietal lobe is especially related to a high order of intellect, and, we may assume, to genius and constructive imagination. If we compare the occipital lobe in man and the anthropoid apes, we find that in man there are four annectant gyri, to connect the parietal lobe with the occipital—parieto-occipital annectants—two connect the temporal—occipito-temporal. The latter two exist in all primates, small in the lower apes, more developed in the anthropoid apes, and still more developed and much more sinuous in man: they form the anatomical substratum of the association of hearing and vision.

The former two are of more importance morphologically; the first occipital corresponds to the upper border of the hemisphere, and unites the superior parietal and first occipital. The second parieto-occipital gyrus extends from the angular gyrus to the second occipital. In the human brain both these two annectant convolutions are well developed and superficial. They are met with in a great number of anthropoids, but one of them only is superficial, the other is deeply situated. The difference then between the anthropoid brain and the human is not so much in the occipital lobe as in the parietal, for we find in the anthropoid brain a well-developed region corresponding to the inter-medial zone of Flechsig. It is in the parietal region that the great development of the posterior part of the brain has occurred, the region in which Flechsig locates the concept centres.

Now, Elliot Smith has shown in some very valuable and interesting papers that the cortex in man may, in the case of some races, such as the Fellaheen and Soudanese, relatively frequently possess anatomical features as regards the position of the striate region and the calcarine fissure on the external surface of the occipital lobes, akin to that of the anthropoid apes, and especially to that of the gorilla. I have also found this condition very frequently in the brains of people dying in the asylums, in the brains of Chinamen, of a Goanese, a Congo negro, and of an Egyptian, and even a certain number of people who have died in Charing Cross Hospital. The calcarine fissure extended in these instances for a considerable distance around the pole of the hemisphere, and the striate area had a distribution somewhat similar to that in the anthropoid ape. Now, without going into minute anatomical details, we may assert that Elliot Smith is probably correct in assuming that the "*affenspalte*" is not the exclusive property of the ape's brain, but that it is represented, and certainly is present in a large number of human brains, either in the form of a definite sulcus lunatus, delimiting the striate area, or in the form of the sulcus lateralis, which is the lunatus displaced. In a great majority of European brains the striate area only extends to the pole

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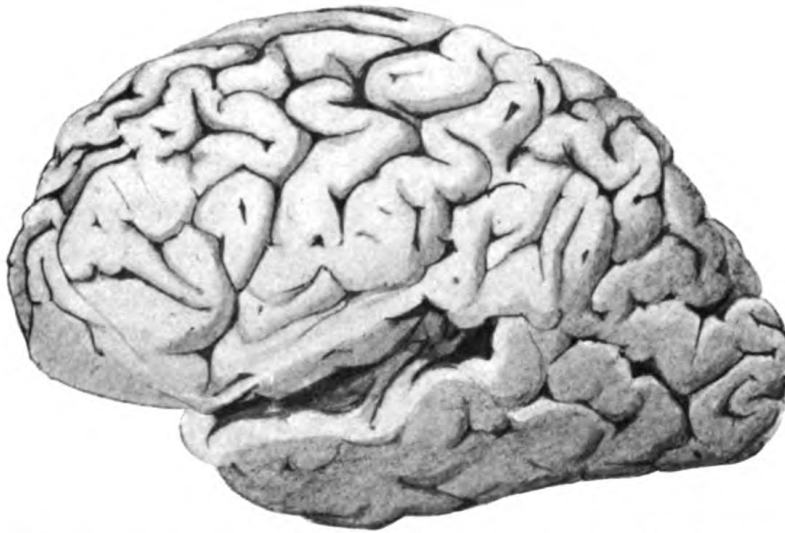


FIG. 28.—*The left hemisphere of a brain in which the posterior extremity of the retro-calcarine fissure extends round the caudal pole 8 mm. on to the lateral surface. The parietal development of this hemisphere was poor compare with the right hemisphere, fig. 29).*

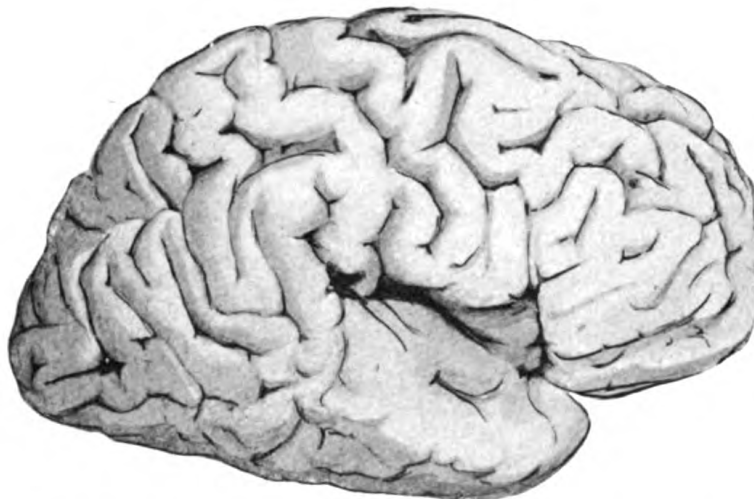


FIG. 29.—*The right hemisphere of the same brain. In this hemisphere the parietal lobe is more highly developed. The occipital area has therefore been pushed backwards on to the mesial surface; and the retro-calcarine does not appear on the lateral surface.*

Face p. 31



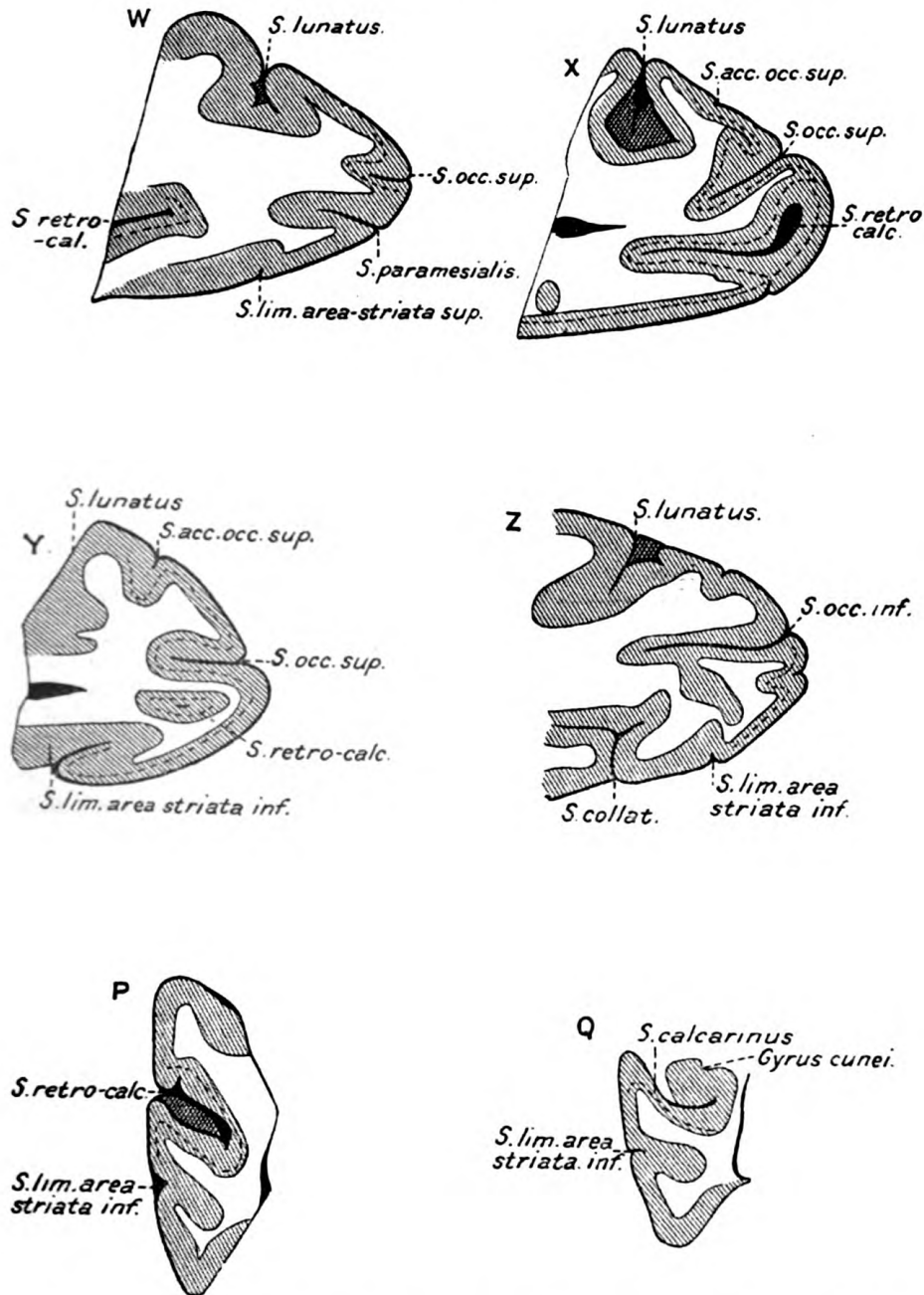


FIG. 32.—Drawings of sections of the occipital lobe of the left hemisphere through the lines W, X, Y, Z, P, Q, figs. 30 and 31. By this means the distribution of the area striata was mapped out on the mesial and external surfaces of the occipital lobe, and its relations to the various sulci, according to the nomenclature of Elliot Smith, are indicated.

FIG. 30.—*Occipital lobe. Left hemisphere. Lateral surface.* The posterior extremity of the retro-calcarine extends 8 mm. on to the lateral surface, where it joins the inferior branch of the "V" shaped superior occipital sulcus. The lunate sulcus is about 28 mm. from the caudal pole, and is placed obliquely; beginning superiorly just below the dorso-lateral border; and joining the sulcus occipitalis inferior lower. The prelunate sulcus branches forward from it about half way down. Lying between the sulcus occipitalis superior and the sulcus lunatus there is a sulcus accessorius occipitalis superior, parallel to the lunatus, and hooking round the point of junction of the two limbs of the sulcus occipitalis superior.

FIG. 31.—The retro-calcarine lies in an almost horizontal line about one third of the way down from the dorso-mesial border. It joins the more obliquely placed calcarine fissure at its junction with the parieto-occipital. The calcarine proper or stem is only about 10 mm. long. The retro-calcarine is bordered above by the sulcus limitans area striata superior; and below by the sulcus limitans area striata inferior. The sulcus paramesialis lies on the mesial surface close to the dorsal border.

The nomenclature adopted by Elliot Smith is followed in this description.

Extent of the Area Striata.—On the mesial surface the area striata does not extend anteriorly further than the junction of the parieto occipital fissure with the calcarine fissure. It is found on the lower lip of the calcarine (stem) and here it extends only 6 mm. forward (fig. 31.). Just behind this point the striate area crosses the base of the fissure and is found on the lower edge of the cuneus, but it does not extend to the "sulcus limitans area striata superior." It curves round the caudal pole to the lateral surface, the posterior end of the sulcus paramesialis marking its superior boundary. Below the retro-calcarine fissure the area striata is bounded by the sulcus limitans area striata inferior.

On the lateral surface the striate area is bounded *superiorly* by a line drawn across the superior extremity of the sulcus occipitalis superior—the accessory superior occipital sulcus; *inferiorly* by a line drawn from the superior extremity of the inferior occipital to a point just below the accessory superior occipital sulcus; and *anteriorly* by a line following the curve of the sulcus lunatus, and about half way between that fissure and the sulcus accessorius occipitalis superior.

If these diagrams be studied it will be observed that an expansion of the parietal lobe would tend, provided there was not corresponding expansion of the occipital portion of the calvarium, to press back this striate area (which forms the primary half vision centre) on to the mesial surface, in such a way that the superior accessory occipital sulcus would become the vertical fissure of Seitz; and the little convolution which lies between it and Elliot Smith's superior occipital sulcus would become the posterior cuneo-lingual gyrus. This sometimes is superficial, more often deeply situated. When it is superficially situated, the striate area extends considerably beyond the pole, even when this convolution is on the mesial surface. The result of the pushing back would lead to an increased extension of the striate area on the superficial mesial surface of the cuneus, so that it would extend upwards to the "sulcus limitans area striata superior" (Elliot Smith), and this would give rise to an expansion upwards of the cuneate lobe, and alter its shape to that indicated on the diagram by the dotted line.

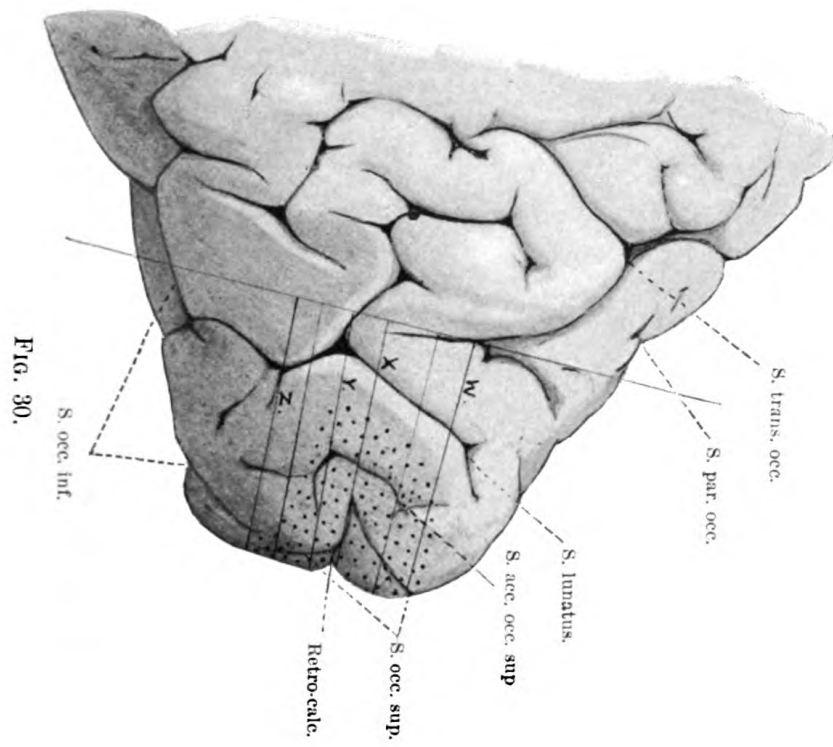


FIG. 30.

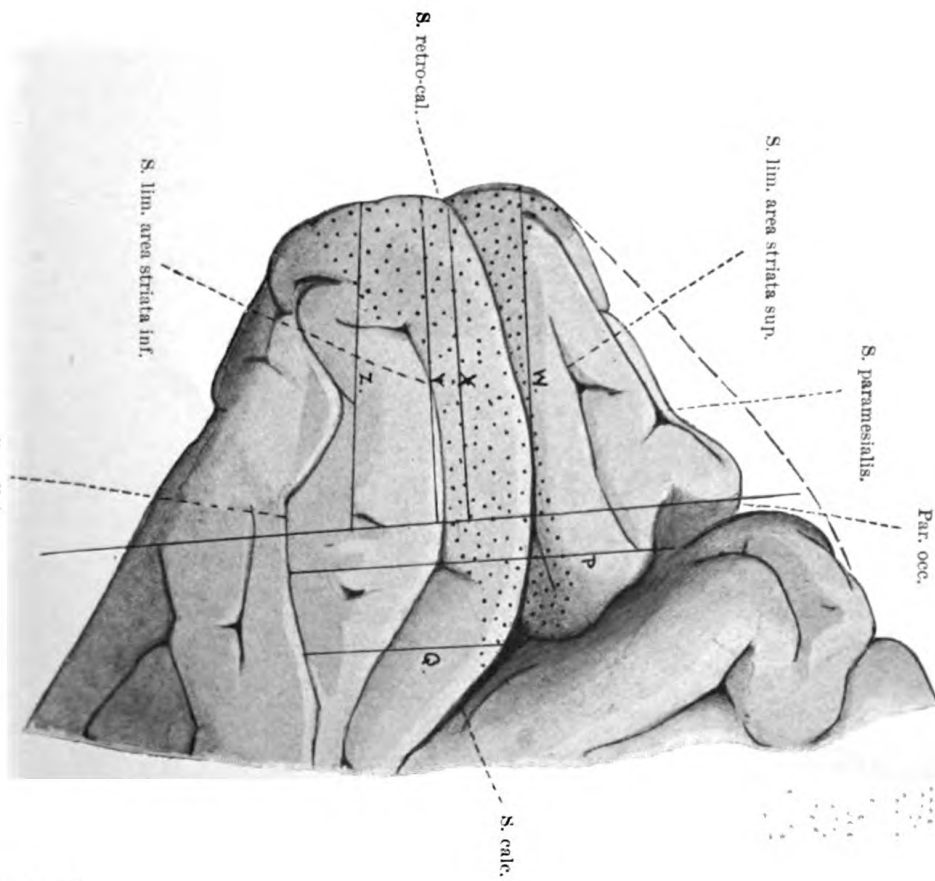


FIG. 31.

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of the occipital lobe ; the calcarine fissure (retro-calcarine of Elliot Smith) terminates in the vertical fissure of Seitz, and all gradations of distribution of the placement of the striate area may be found between the extreme form which resembles the anthropoid brain, with a definite sulcus lunatus, and the highest human type with the striate area terminating at the pole. This anthropoid type I have, like Elliot Smith, found much more often in the left hemisphere than in the right.

Since this lecture was written I have examined, in conjunction with my assistant, Dr. Watson, over 100 brains, and have found that in 25 per cent. the calcarine fissure and the striate area extends on to the external surface from 18 to 30 mm., and there is a definite lunate sulcus in the majority of them. The brains were those of lunatics dying in the asylum. As a rule, where this condition persisted in the left hemisphere and not in the right, there appeared to be a better parietal development on the right than the left (*vide* figs. 28, 29, 30, 31, 32). Occasionally it was present in both occipital lobes, and then there was generally a deficiency of parietal development on both sides. Moreover, generally speaking, the brains of patients from the intellectual classes showed the termination of the calcarine fissure in the vertical fissure of Seitz well within the mesial surface of the pole, and in such cases the parietal development was good on both sides. Dr. Duckworth has published the examination of the brains of three Australian aborigines, and shown that this anthropoidal type of occipital lobe exists, which agrees with my experience that as a rule (though by no means invariably) such an appearance of the occipital lobe on one or both sides is associated with a brain below the average in weight and convolutional pattern such as occurs so frequently in congenital aments.

We have now to consider what are the functions of the two histologically, phylogenetically, and ontogenetically different regions of the occipital lobe.

V. EXPERIMENTAL AND CLINICO-ANATOMICAL OBSERVATIONS.

A dog from which the eyeballs were removed two days after birth by von Monakow was able to behave some months afterwards as an ordinary dog; its orientation was perfect, contrasting therefore markedly with the dog which had had both visual cortical spheres removed, and in which orientation was very defective. Peripheral blindness in the human being is accompanied by an increased tactile kinæsthetic sensibility by which orientation is carried on, contrasting markedly with cortical blindness. The remarkable cases of Helen Keller and Laura Bridgeman, who became blind and deaf in early infancy and yet, by appropriate education, attained a high degree of intelligence, and were able apart from vision to live the lives of normal individuals, shows that sensory visual impressions are but a part of visual perceptions.

I have already alluded to the fact that Simians alone possess stereoscopic macular vision. Are we right in assuming that the whole of the fibres of the optic radiations, including the macular fibres, terminate in the region which is delimited by this characteristic histological structure of cortex? Von Monakow, whose work upon cerebral pathology, and especially that relating to the functions of vision, entitle him to a foremost place among accurate observers and philosophical thinkers, is of opinion that experimental and clinico-anatomical observations in man conclusively show that the macular impressions concerned with central, and therefore distinct vision are received by the whole occipital lobes of both hemispheres. He even would not limit reception of macular impressions to the occipital lobe but would include the angular gyrus as well. Henschen, another great authority, and one who has devoted a large amount of time to careful clinical and anatomical observations, besides reviewing all the recorded cases of hemianopsia and blindness resulting from cerebral lesions, is of opinion that there is a cortical retina, and that this cortical retina is the area bounding the calcarine fissure and its lips; and that the lower half of this calcarine region corresponds with

the lower quadrants of the homonymous halves of the two retinae, the upper to the upper; and that a definite portion of the calcarine cortex corresponds to the macula. He very rightly points out that there is no recorded case of lesion of the occipital lobe producing hemianopsy in which the calcarine region is not involved. Moreover, he brings forward cases in which hemianopsy of the lower quadrants of the retinae were associated with softening of the lower half of the calcarine region, and cases of softening of the upper half of the calcarine region with hemianopsy of the upper quadrants of the retinae.¹

Henschen affirms in contradiction to Monakow that it is possible owing to the vascular distribution to have a localised softening of this calcarine cortex without destruction of the subjacent optic radiations; and he has brought forward cases to prove this with anatomical preparations. His opinions would be strongly supported by Flechsig, for he locates by myelination methods the primary visual area to the calcarine cortex. The strong point in the argument in favour of von Monakow's opinion is the record of several cases of which careful clinical and perimetric observations were correlated with careful anatomical researches. Notably the classical case of Förster with an anatomical examination by Sachs. In this case there was during life preservation of central vision on both sides, although there was a bilateral homonymous hemianopsy. The anatomical research of Sachs showed that one occipital lobe was

¹ A case recently published by Drs. Beevor and Collier was considered by the authors to support the view of von Monakow. By the courtesy of these gentlemen I was able to see the sections, and they agreed with me that if by the calcarine cortex Henschen means the striate area, then there was sufficient left of the striate cortex on the upper lip of the calcarine fissure and the mesial surface of the cuneus to account for the preservation of vision in the lower quadrants of the hemianopic field of vision, as shown by the perimetric charts. In fact, the case illustrates very conclusively to my mind the truth of Henschen's views. This only shows another example of the possible variability of the infolding of the striate area, and that instead of speaking of the calcarine cortex being the half-vision centre, it would be better to speak of the striate area as the half-vision centre, for we have seen that it may extend in some cases a considerable distance on to the external surface of the hemisphere.

entirely destroyed, in the other it was in great part destroyed; a small portion of the calcarine fissure in front and a small portion behind being left intact. Both Henschen and Monakow use this case as an argument in favour of their respective views; the former asserting that the preservation of central and macular vision was due to the integrity of the anterior portion of the calcarine cortex, which was preserved owing to special vascular supply. The difficulty of the fact that central vision was preserved on both sides Henschen overcomes by accepting Wilbrand's hypothesis that the macular fibres of the optic nerve bifurcate, and therefore each macular region is connected with both external geniculate bodies. Thus the preservation of this portion of the cortex would allow of visual perception from both central regions of the retina. It might be argued why should it not have been in this case the posterior intact piece of calcarine cortex which retained macular perception? Sachs himself does not support the view which was put forward by Förster that the retention of central vision was due in this case to the macular region receiving a separate blood supply.

It should be mentioned that Förster and Sach's case showed loss of memory pictures and orientation, and observers, since the facts were published, have sought for these symptoms in cases of bilateral hemianopsy. A notable and important case is that of Schmidt and Laqueur. The patient suffered with double hemianopsy, but central vision was so far preserved that he could even read and write, but, as regards orientation, he behaved like a blind man; moreover, he had a loss of memory pictures. In this case, there was softening of the whole of the striate calcarine region of one occipital lobe, leaving, however, a considerable portion of the remainder of the occipital lobe intact. The other occipital lobe was destroyed except about 200 square mm. of the posterior calcarine region. Now, Edinger has recorded a case in which complete blindness resulted from bilateral destruction of the occipital lobes. We may, therefore, assert that the retention of central vision in the two cases mentioned was due either

to the intact posterior calcarine cortex, or, if we accept Monakow's view to all the remaining intact occipital cortex. Bernheimer's work is quoted by Monakow to support his views, for this observer found that the macular fibres are intimately mingled with the others, and spread out in a wide area of distribution in the external geniculate body; it is therefore presumable that it has no definite cortical localisation. Monakow and Dejerine assert that the pulvinar, to which some of the optic fibres proceed, stands in close connection with the gyrus angularis. The progressive development of the visuo-psychic zone in mammalia, its appearance as a definite zone in the primates coincident with a macula, eye movements independent of head movements, and convergent binocular stereoscopic vision, support the view of Monakow that the macular fibres end in this zone as well as the primary visuo-sensory area. Admitting this, we can understand why almost total destruction of the calcarine region on both sides does not produce central blindness, whereas, as Edinger's case shows, successive destruction of both occipital lobes produced at first hemianopsy, then complete blindness. Clinico-anatomical facts support, in my opinion, the view of Henschen that the upper quadrants of the right halves of the two retinae are projected on to the upper half of the right striate cortex, the lower quadrants to the lower; similarly the left to the left striate cortex. The macular localisation, however, by clinical observation is not yet satisfactorily determined. We can only wait further carefully recorded cases, although even here we meet with the difficulty emphasised by von Monakow that one is never certain how far the symptoms observed may be due to subcortical destruction.

Again, while admitting the great value of the pioneer experiments of Munk and Schäfer, yet, even when performed upon apes, there are several fallacies—notably that of testing remaining vision in animals, but also it will be seen, from reference to fig. 17, in which the visuo-sensory region is delimited, that it is impossible to destroy the whole striate area in the monkey without destroying a

large part of the visuo-psychic cortex which it overlaps and joins. Schäfer found that only after complete removal of all the brain behind the *affenspalte* was blindness produced in *Macacus*; this would mean destruction of the whole visuo-sensory and visuo-psychic region (adopting the terms of Bolton and Campbell). It may, however, be remarked that Schäfer, from the movements elicited by excitation of different portions of the striate surface of the occipital lobe in apes, concluded that the retinæ are projected on the cortex. All observers have found that movements of the eyes are much more easily elicited by stimulation of the mesial surface of the occipital pole; in fact, with a relatively weak current, I found this was the only excitable part of the striate cortex. Sherrington and Grünbaum note this fact in anthropoid apes, although the observations of Campbell show that the striate cortex extends a considerable distance further forward on the external surface. This fact may owe its explanation to stimulation by the current of a larger area owing to the involution of cortex by the calcarine fissure, or those who favour macular localisation might assert that the facts favour the idea of the macular fibres terminating in an area of cortex which is provided with the most motor neurons.

To continue the argument, macular vision, to be effective, requires appropriate motor adaptation for fixation of the visual axes. There are, however, two pairs of cortical regions which control movements of the head and eyes—occipital and frontal: the former, which may be looked upon as representing Hughlings Jackson's middle level, forms the second reflex circle, the first lowest being the retinal light reflex by the corpora quad, unconscious and involuntary; whereas the second reflex circle, by way of the occipital lobes, we may term, with Munk, visual reflexes—reflexes which occur without thought or attention, such as blinking the eye upon the sudden approach of the hand, turning aside of an animal when an obstacle is placed in its way, flight on approach of danger, and those unconscious movements which are necessary for the fixation of an object

perceived at first indistinctly. These reflexes are of an inferior order, and do not imply any higher mental representations. The movements only occur upon the occasion of visual sensations.

The third reflex circle, which, corresponding to Hughlings Jackson's highest level or Munk's acquired visual reflexes, involves reflection and attention; it is effected by macular vision and fixation of the eyes, the visual impressions are fused, with tactile, kinæsthetic and auditory images revived by association. The excitation of the visual cortex extends to some portion or the whole of the circumjacent visual association zone, from which it can spread to all parts of the cerebral cortex, but the defined lines along which it will spread depend upon the fusion with past experiences in associative memory. The corollary to this statement is that the visual directive faculty must progress coincidently with the extension of this circumjacent zone of association by virtue of the increased possibilities of associative memory.

About thirty cases of bilateral hemianopsy have been recorded, and in none were disturbances of voluntary eye movements observed. This can be explained by the fact that experiment has shown the existence of a centre for eye movements in each frontal lobe. In apes, the area which on stimulation gives rise to movements of the eyes, lies close in front of the precentral sulcus (*vide* fig. 33). Stimulation causes always associated head and neck movements. Horsley and Beever's, also Sherrington's and Grünbaum's, experiments on the anthropoid apes show that the region which, upon excitation, produces movements of the eyes, occupies an area of considerable extent in front of the external surface of the frontal lobe, separated by an inexcitable zone from that which gives rise to head and neck movements and opening and closing of the eyes (*vide* fig. 34). Presumably the same thing obtains in man, and probably the same cause which has led to the pushing back of the striate area of the occipital lobe already described has brought about this change in the frontal lobe. We may associate it with the more

complete dissociation of the fore-limbs from progression and the erect posture.

It is a suggestive fact, showing reciprocal simultaneity in

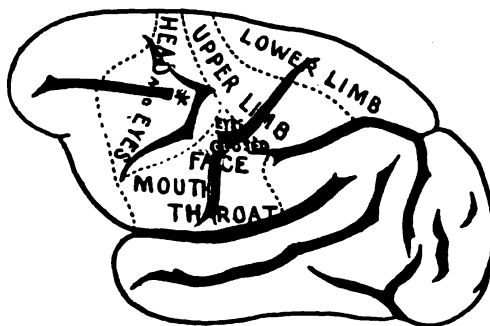


FIG. 33.

Diagram after Schäfer of the brain of macacus, showing the regions which, on excitation, give rise to motor response. *The angle of the precentral sulcus where stimulation invariably, and with a weak current, gives rise to conjugate lateral deviation of the head and eyes. There is no inexcitable region intervening as in the anthropoid brain. In conjunction with Professor Halliburton I have shown that the excitable motor area does not extend, as represented in this diagram, behind the central fissure. It conforms, therefore, in this respect with that of the anthropoid ape.

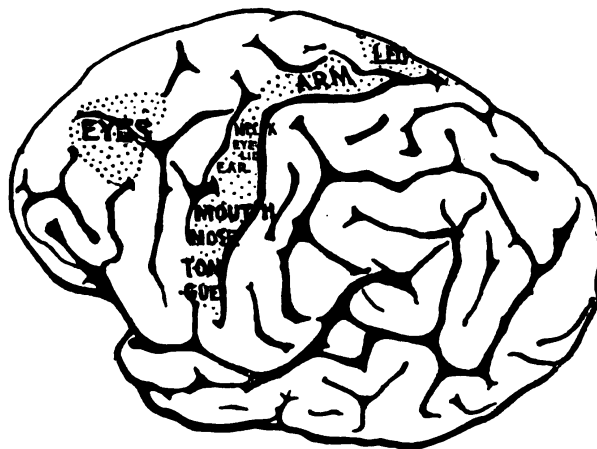


FIG. 34.

Diagram from photograph of the brain of chimpanzee, in which the excitable area was mapped out by Sherrington and Grünbaum. It will be observed that there is a wide area, the stimulation of which gives rise to eye movements, and that a considerable intervening area exists which gives no motor response on faradisation.

the development of the visual directive and the tactile motor executive faculties that the near point of distinct vision corresponds with the most mobile position of the hand.

Now, all parts of the cortex which have sensory functions are also motor. It has been shown in apes that excitation of the frontal eye-centres produces movements of the eyes when the occipital lobes have been separated, and Munk showed that an animal which had long suffered from cortical blindness from ablation of the occipital lobes still yielded on excitation of the frontal eye-centres the same movements.

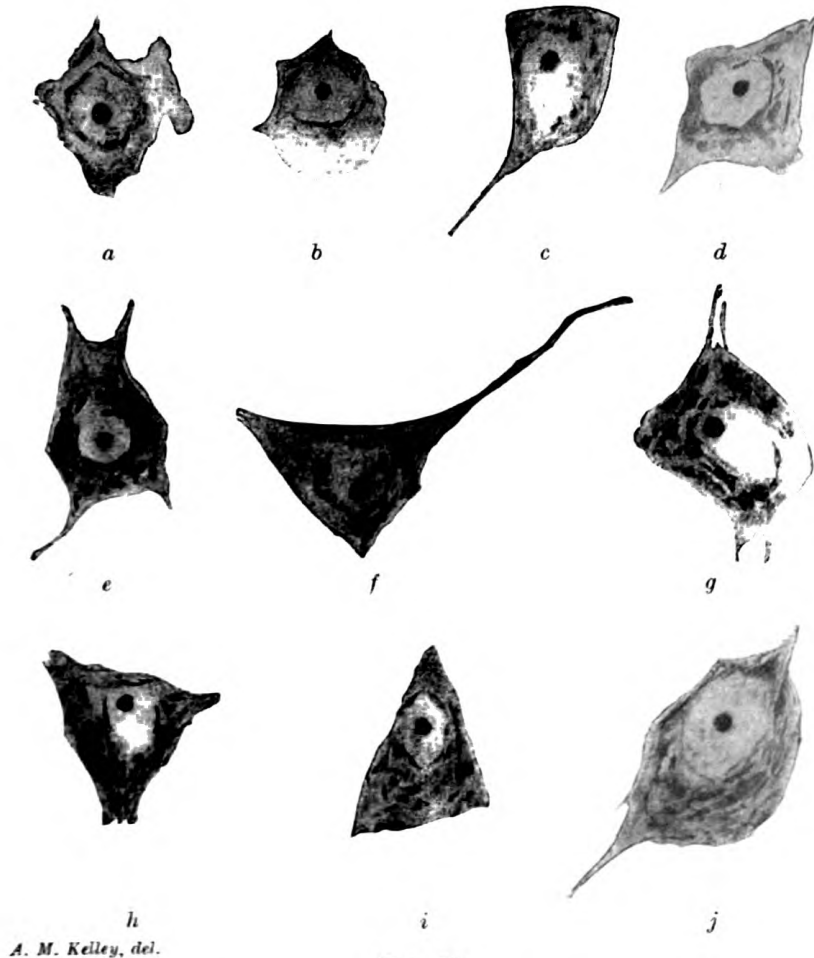
It may, therefore, be presumed that these centres can act independently of vision. What then is the sensory path? Presumably the fifth nerve, and the upper sensory branches of the cervical cord supplying the head and neck. But there is considerable evidence to show that the frontal lobe is concerned with the maintenance of gait and station, by its connection by afferent and efferent paths through the thalamus and red nucleus to the opposite lateral lobe of the cerebellum. This is supported by the fact that one of the most characteristic signs of large tumours involving the frontal lobes is ataxy. There is evidence likewise to show that a large bundle of association fibres passes from the occipital lobe to the frontal lobe, the superior longitudinal bundle; these fibres, without doubt, arise from the large pyramidal cells of the third layer of the association zone. May not, therefore, this area, which has been shown in the anthropoid ape's brain to be inexcitable, consist of a zone of cortex which serves for the fusion of visual, equipoisal sensations, and those coming from the head and neck, trunk, and specially lower limbs? As the erect posture develops in the primates, the motor adaptations necessary for gait and station become more complex, and vision as a directive faculty plays a more important part. Not that the whole of the association fibres which pass from the occipital lobe to the frontal lobe are concerned with this function in the anthropoid ape, for a large number must serve for the association of the eye and hand. If, therefore, this associational zone of the occipital lobe which we have seen increases *pari passu* with the erect posture be destroyed, it should produce a loss of orientation, for visual impressions can no longer be associated with kinæsthetic images

of gait and station. One of the most interesting facts that we can make out from a study of the published cases of bilateral hemianopsy is that loss of memory pictures and orientation frequently occur. It was so in Förster's case, but this loss does not appear to stand in relation to the amount of the visual defect as such. For whereas in the case of Grönouw the loss of orientation was as profound as in Förster's case, the visual defect was very much less. In Schmidt and Laqueur's case the man was able to read well, write fairly, and converse rationally, but he was unable to find his way in his own house, to find the bed in his room, or the chair he was about to sit on. Since cases have been recorded in which hemianopsy was present, without loss of visual memory pictures, and a case has been recorded by Charcot in which there was loss of optic memory pictures without hemianopsy, we must conclude that there is a different location for the two functions. Likewise the fact that cases have been recorded of hemianopsy in which visual hallucinations have occurred on the hemianopic side, shows that the memory pictures are formed in some region other than the striate cortex. Very frequently, however, it happens that hemianopsy and loss of optic memory pictures are combined; it follows, therefore, that localisation of the two functions are probably in adjacent areas.

Now it has already been shown that homonymous visual defects are due to disease and destruction of the striate cortex. Disturbances of orientation are due then to lesions of the remainder of the occipital cortex containing the large pyramids. In all cases in which the continuous disturbances of orientation and memory pictures exist, lesions have been found in both occipital lobes; in those cases of disturbance of orientation in which there was only unilateral hemianopsy, there were bilateral lesions of the occipital lobes, but the striate cortex was only destroyed on one side.

By virtue of the callosal commissural connections, the two occipital lobes habitually act together, therefore destruction of one lobe produces no loss of orientation.

Psychical disturbances after bilateral lesions of both occipital lobes are characterised by affection of the optical components of images, and by disturbances of orientation.



A. M. Kelley, del.

FIG. 35.

FIG. 35 shows the average-sized solitary cell of Meynert, selected from ten examples in specimens of the visual cortex of the animals named, drawn to a scale under a magnification of 500. *a.* Hedgehog. *b.* Guinea-pig. *c.* Rabbit. *d.* Pig. *e.* Camel. *f.* Suricate. *g.* Cat. *h.* Dog. *i.* Monkey (visuo-sensory). *j.* Human (visuo-psychic area).

There may be all grades of this affection, commencing with the simple difficulty of interpreting the retinal pictures and associating them with acquired experiences. The disturb-

ance may extend to a complete loss of the faculty of identifying the common objects of daily life, and such disturbances may exist in spite of well-marked visual acuity and the retention of stereognostic sense. This loss of function is associated with destruction of this later phylogenetically and ontogenetically acquired cortex—a cortex which we have seen progressively increases in the primates, as we rise in the scale. Moreover, the large cells and fibres which are characteristic of this cortex are especially large in the human brain as compared with the apes, in my opinion, larger in proportion than could be accounted for by difference in the size of the brain; for I have not found so much difference in the size of the solitary cells of Meynert. Campbell has told me that he has observed, as I myself have noticed, that the visuo-psychic cortex in the cat, dog, and pig is only present as a thin zone along the lateral margin of the visuo-sensory area. It is structurally not nearly so distinct as in man; the fibre wealth fades insensibly into surrounding parts, and, although large pyramidal cells can be seen at the right level, they do not show the same degree of resemblance to the corresponding human elements as the solitary cells of Meynert.

In fig. 35 is represented the averaged-sized solitary cell of Meynert found in the visual cortex of a series of different orders of mammals. It will be observed that the cells do not show a marked difference in size, although the length of the axon in the camel and the guinea-pig must be very different.

VI. SOME FURTHER HISTOLOGICAL DETAILS REFERRING TO INDIVIDUAL CELL STRUCTURE.

The researches of Bethe and Cajal have shown that the nerve cell possesses fibrils, which extend from the dendrons through to the axon, and it appears to me that the size of the cell depends not so much upon the length of the axon, as upon the number of fibrils which are contained in the neuron, and which serve as points of contact with other neurons. Since the solitary cells of Meynert are phylo-

genetically and ontogenetically earlier developed (in fact, these cells can be seen in the foetal cortex at the sixth to seventh month), they are in connection with and preside over lower neurons of practically similar functional value in all the higher mammalia, innervating as they do, similar groups of neurons presiding over similar groups of muscles; therefore, if size and number of fibrils and not length of axon determines the form and size of the cell we can understand why these motor cells in the visual cortex should vary so little in size in different animals.

SUMMARY.

The cortex in the following orders of mammals was examined: (1) Insectivora; (2) Rodents; (3) Marsupials; (4) Ungulates; (5) Carnivora; (6) Lemurs; (7) Primates.

The following conclusions were arrived at: There is a correlation of structure and function as exhibited by a progressive complexity of cell lamination of the visual cortex in mammalia from the insectivora to primates. The more the animal depends on vision as a directive faculty in its preservation the more complex is the structure.

The transition of unioocular panoramic to perfect binocular stereoscopic vision shows successive stages in the number of direct fibres until, in the primates, there is semi-decussation, and, as far as my observations go, this may be correlated with a progressive development in the layer of higher associational pyramidal cells lying above the layer of granules.

The progressive evolution of vision as a directive faculty is simultaneous with a motor adaptation, especially related to the mode of feeding and defence rather than to a particular species.

Carnivorous animals, especially cats, therefore, have their eyes set forward, abundant direct fibres, and good binocular vision, to enable them to seize their rapidly moving prey with their teeth or paw.

Better motor adaptation as Sherrington has independently suggested from his flicker observations then is prob-

ably the essential cause of the direct path of the optic fibres and binocular vision.

It is, however, in the primates that we have semi-decussation of the optic fibres, a macula lutea, eye movements in all directions independent of head movements. Convergence and perfect binocular stereoscopic vision associated with the hand, which, in the apes, becomes the principal executive agent in the procuring of food, defence, and flight. Visual images are now always associated with impressions of the exploring hand and the ideas of form, substance, extension, and qualities of objects are the complex of the visual and tactile kinæsthetic images and capable of endless variations. This we may connect with the appearance in the zoological series of an occipital lobe, a line of Gennari visible to the naked eye, a deep layer of pyramids with a double layer of granules in the visuo-sensory striate area. But even more important than this is the appearance of a definite associational zone in which there is a much greater depth of pyramidal cells, the third layer of which is characterised by very large pyramids serving as higher complex association neurons between the visual cortex and the auditory and tactile motor areas. As we rise in the scale of primates this associational zone increases with the more perfect specialisation of the forelimbs for manipulation and the erect posture, and this we may correlate with the increase in area of the associational or visuo-psychic zone the increasing development of the parietal lobe, and the pushing back and infolding of the striate visuo-sensory cortex, so that in the highest types of man it comes to occupy the infolded calcarine region of the mesial surface, although some lower types still preserve the anthropoidal character. It is probable that the same causes give rise to the shifting forward of the anterior motor eye centres.

BIBLIOGRAPHY.

- (1) ANTON AND ZINGERLE. "Die Leistung und Erkrankung des Menschlichen Stirnhirnes."
- (2) BASTIAN. "Brain as an Organ of Mind."
- (3) BECHTEREW. "Ueber das Sehfeld an der oberflaeche der Grosshirnhemisph," *Neurol. Cent.*, 1890.

- (4) BROADBENT. Jacksonian Lecture, *Brain*, 1904.
- (5) BEEVOR AND COLLIER. "A Contribution to the Study of the Cortical Localisation of Vision," *Brain*, Part II., 1904.
- (6) BOLTON, J. S. "The Exact Histological Localisation of the Visual Area of the Human Cerebral Cortex," *Phil. Trans.*, vol. cxci., 1900.
- (7) RAMON Y CAJAL. Nouvelles Contributions à l'étude histol. de la retine et à la question des anastomoses des prolongements protoplasmiques: (1) *Journal de l'Anat. et de la Physiol.*, 1896, No. 5; (2) "Etudes sur l'écorce cérébrale de l'Homme et l'Ecorce visuelle," 1900.
- (8) CAMPBELL. "Histological Studies and Cerebral Localisation," *Proceedings Roy. Soc.*, vol. lxxii.
- (9) CUNNINGHAM. (1) Presidential Address Anthropol. Section of British Association, 1901; (2) "Contribution to the Surface Anatomy of the Cerebral Hemispheres," Roy. Irish Academy, "Cunningham Memoirs," No. 7, 1892.
- (10) DUVIGNEAUD (ROCHON). "Anatomie de l'Appareil Nerveux Sensoriel de la Vision."
- (11) DEJERINE. "Anatomie des Centres Nerveux."
- (12) EDINGER. (1) "Bau der Zentral Nervenorganen"; (2) *Deutsche Archiv f. Nerv.*, p. 265.
- (13) FLECHSIG. Gehirn und Seele, "Einige Bemerkungen über die Untersuchungsmethoden der Grosshirnrinde insbesondere der Menschen," 1904.
- (14) FÖRSTER AND SACHS. Förster: "Ueber Rindenblindheit," *Graefe's Archiv. f. Ophthalmol.*, Leipzig, 1890; Sachs: "Das Gehirn des Försterchen Rindenblinden Arbeiten aus Psychiat. Studien in Breslau herausgegeben von Carl Wernicke," Leipzig, 1825, 5389.
- (15) GRÖNÖUW. *Archiv f. Psychiatrie*, 1891, p. 339.
- (16) GOWERS, SIR WM. "Subjective Visual Sensations," Bowman Lecture.
- (17) HARRIS, WILFRED. "Binocular and Stereoscopic Vision in Man and other Vertebrates, with its Relation to the Decussation of the Optic Nerves, the Ocular Movements, and the Pupil Light Reflex," *Brain*, Spring Number, 1904.
- (18) HENSCHEN. "Revue Critique de la Doctrine sur le Centre Cortical de la vision," a valuable monograph summarising all the knowledge of the subject derived from clinico-anatomical reports.
- (19) HITZIG. *Neurolog. Centralblatt*, vol. xxi., 1902.
- (20) HORSLEY AND BEEVOR. "A Record of the Results obtained by Electrical Excitation of the So-called Motor Cortex and Internal Capsule in an Orang-outang (*Simia satyrus*)," *Phil. Trans.*, 1890-91, B, p. 129.
- (21) JAMES. "Principles of Psychology."
- (22) JACKSON, HUGHLINGS. "The Evolution and Dissolution of the Nervous System," Croonian Lecture, 1884.
- (23) KELLER, HELEN. "The Story of My Life."
- (24) KUSTERMAN. "Ueb. doppelseit. homon. Hemian, &c.," *Monatssch. f. Psych. und Neurol.*, vol. ii., fasc. 5.
- (25) KNIES. (1) "Ueber die centralen Störungen der Willkürlichen Augenmuskeln," *Knapp Schwesigger's Archiv f. Augenheilkunde*; (2) "The Eye in General Disease," translated by Henry Noyes.
- (26) JOHNSON, LINDSAY. "The Comparative Anatomy of the Mammalian Eye," *Phil. Trans. Roy. Soc.*, vol. cxci., B, 1902.
- (27) MOTT AND SCHÄFER. "Associated Eye Movements Produced by Cortical Faradisation of the Monkey's Brain," *Brain*, vol. xvii.

- (28) MUNK. (1) "Sehsphäre und Augenbewegungen Sitzungsberichte der Königl. preussisch," *Akad. der Wissenschaft zu Berlin*, 1890; (2) "Sehsphäre und Raumvorstellung," *Beitr. z. Wissensch. Med.*, 1891; (3) "Ueber die Function der Grosshirnrinde," Berlin, 1890.
- (29) OBREGGIA. "Ueber Augenbewegungen auf Sehsphärenreizung," *Archiv f. Anat. und Physiol.*, 1890.
- (30) RETZIUS. "Das Menschengehirns."
- (31) SCHÄFER. "Functions of the Brain," "Text-Book of Physiology," vol. ii.
- (32) SCHMIDT AND LAQUEUR. "Ueber die Lage des Centrums der Macula lutea in Menschlichen Gehirn," *Archiv f. Path. Anat.*, 1899.
- (33) SHERRINGTON. "Binocular Flicker and the Correlation of Activity of Corresponding Retinal Points," *British Journal of Psychology*, vol. i., part i.
- (34) SHERRINGTON AND GRÜNBAUM. "Observations on the Physiology of the Cerebral Cortex of the Higher Apes," *Proc. Roy. Soc.*, vol. lxxix. B.
- (35) RUDINGER. "Ein Beitrag zur Anatomie der Affenspalte und der Interparietal furche beim Menschen nach Rasse," "Geschlecht und Individualität," Bonn, 1886.
- (36) SOURY. "Le Cerveau," "Dictionnaire de Physiologie" (Richet); an admirable summary of the evidence and bibliography appertaining to the localisation of function in the cerebral cortex.
- (37) STEINER. (1) "Sehsphären und Bewegungen," *Pflüger's Archiv. f. Phys.*, 1891. (2) "Ueber die Entwicklung der Sinnesphären insbesondere der Sehsphäre auf der Grosshirnrinde des Neugeborenen," Sitzungsberichte und König. preuss. *Akad. der Wissenschaft*, Berlin, 1895, 303.
- (38) SMITH, ELLIOT. (1) "Studies in the Morphology of the Human Brain, with Special Reference to that of the Egyptians: No. 1, The Occipital Region," Cairo, 1904; (2) "The So-called 'Affenspalte' in the Human (Egyptian) Brain," *Anatomischer Anzeiger*, Band 24; (3) "Catalogue of the Museum of the Royal College of Surgeons."
- (39) SPENCER, HERBERT. "Principles of Psychology."
- (40) TESTUT. "Traite d'Anatomie."
- (41) VON MONAKOW. (1) "Gehirn Pathologie"; (2) "Ueber den gegenwärtigen Stand der Frage nach der Localisation im Grosshirn," *Ergebnisse der Physiologie* (In this will be found a most complete bibliography of all that appertains to the subject of cortical localisation).
- (42) VITZNOU. "Effets de l'ablation totale des lobes occipitaux sur la vision chez le chien," *Arch. de Physiol.*, 1893.
- (43) WILBRAND. "Die Doppelversorgung der Macula lutea," *Beitr. z. Augenheilk.*, 1895 (Festschrift Dr. Förster).
- (44) ZUCKERKANDL. "Zur Morphologie des Affengehirns," *Zeitschrift f. Morphologie und Anthropol.*, Band 4, Heft 3, 1902.

THE MAMMALIAN CEREBRAL CORTEX, WITH SPECIAL REFERENCE TO ITS COMPARATIVE HISTOLOGY. I.—ORDER INSECTIVORA.

BY GEORGE A. WATSON, M.B., C.M. EDIN.

*Pathologist to the Lancaster County Asylum, Rainhill; late Assistant to the
Pathologist, London County Asylums.*

INTRODUCTION.

THE results and conclusions brought forward in this paper form a portion of the outcome of an investigation which has already extended over a period of some years dealing with the histological structure of the cortex cerebri of various mammals. A preliminary communication on the subject has already been published in the Proceedings of the Royal Society.

In the course of an enquiry which had an object quite different from the present one, but which necessitated an examination of the cerebral cortex in animals, the writer became more and more impressed with the fundamental importance of Bolton's work upon the functional significance of the cerebral cortical lamination. This author's views were founded upon a study of the order of development of the *human* cerebral cortical layers and of the depth of these, as ascertained by most elaborate micrometric measurements, in various degrees of amentia and dementia, the latter portion of the study being closely correlated with carefully collected clinical data. As Bolton's conclusions, or perhaps it would be more correct to say the methods by which he has arrived at them, have been subjected to a good deal of criticism, it appeared to the writer that a systematic study of the lamination of the neopallium in the mammalian series would prove, *inter alia*, a fruitful source of information concerning the functional significance of the

cortical layers, and would afford important confirmation, or otherwise, of the soundness of Bolton's views, the matter being approached by methods in some respects the same as, and in others different from, those adopted by this investigator.

At the outset of the present research Bolton's conclusions concerning the order of development of the cortical layers in the human subject were confirmed by the writer, and from an examination of the cortex of several foetal and new-born animals it was considered by him that the same order of development holds good for lower mammals. A firm basis for future work appeared to be thus secured.

Bolton's system of classification of the cerebral cortical layers has therefore been made use of in this research—at first only in a tentative manner—and the slight modification introduced was adopted as a matter of convenience, and does not imply any essential alteration in this system.

Leaving aside for the moment Bolton's observations, the writer does not forget the pioneer work in comparative histology of Bevan Lewis, and he by no means wishes to be thought to under-rate the value of the many references to this subject throughout the literature, but so far as he is aware, these have only what may perhaps be justifiably described, as a somewhat fragmentary bearing upon the specific task which he has set himself.*

The above statement sufficiently outlines the primary purpose of this research. It was not at first intended to make a systematic examination of the entire neopallium of any of the mammals belonging to the various natural orders, but in the case of the brains of the Insectivores dealt with in the present paper, this seemed to be necessary for it appeared that no complete examination of these somewhat peculiar neopallia has hitherto been attempted and guiding lines so far as they are concerned were comparatively few. The result has been that maps have been obtained of these

* This investigation was commenced long before Campbell's recently published account of the cerebral cortex in the Cat, Dog, Pig and Anthropoid Apes appeared, and the latter has only an indirect bearing upon the present writer's primary object.

neopallia which are fairly full and it is believed approximately accurate. Further, some facts have thus been brought to light which have an interest beyond that of the primary object of the investigation. In the instances of certain Rodents, Ungulates, Carnivores and Primates advantage can be taken in future work of the excellent maps and descriptions of the cortical areas produced by Bevan Lewis, and more recently by Campbell.

It is not the writer's intention at the present time to attempt any description of the microscopic appearances of the cortex of the pyriform lobe or the hippocampus. It is well known that in the early mammals the olfactory areas form the greater part of the cerebral hemispheres. Elliot Smith* states that "this early predominance of the sense of smell persists in most mammals (unless an aquatic mode of life interferes and deposes it; compare the Cetacea, Sirenia and Pinnipedia for example) even though a large neopallium develops to receive visual, auditory, tactile and other impressions pouring into the forebrain. In the Anthrozoidea alone of non-aquatic mammals the olfactory regions undergo an absolute (and not only relative, as in the Carnivora and Ungulata) dwindling, which is equally shared by the human brain, in common with those of the other Simiidae, the Cercopithecidae, and the Cebidae. But all the parts of the rhinencephalon, which are so distinct in macrosmatic mammals, can also be recognised in the human brain." So far as the writer's observations have gone there is, as might be inferred, relatively little difference in the structure of the archipallium in animals belonging to various orders in the mammalian scale, omitting of course the aquatic mammalia and excluding minor differences of cell form. Hence the archipallium may be considered, with the above mentioned reservations to remain a fairly constant factor throughout the mammalian series. It is naturally far otherwise with the neopallium, the organ developed for the ultimate reception of sensory impressions and for associative memory. The neopallium,

* Catalogue of Royal College of Surgeons' Museum, Phys. Series, Vol. II., p. 467.

as contrasted with the archipallium must necessarily be a very variable quantity, and therefore the more valuable as bearing upon the writer's chief purpose, viz., an enquiry by the comparative histological method into the functional significance of the cerebral cortical layers. For this reason this research is for the time being rigorously restricted to the neopallium.*

Although, as stated, the investigation has already included a more or less complete study of the neopallium of mammals belonging to several natural orders other than the Insectivora, it was thought advisable to publish the results obtained, so far as material became available, under the headings of the various natural orders to which the animals whose brains were examined belong.

The subject of the present paper will be dealt with under the following

HEADINGS :—

BRAINS EXAMINED AND METHODS OF STUDY (p. 53).

MACROSCOPIC APPEARANCES (p. 54).

FURROWS SEEN ON MICROSCOPIC EXAMINATION (p. 56).

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THE NEOPALLIUM.

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Areas of the Neopallium and their Lamination.

I. THE MOLE (p. 63).

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FUNCTIONAL SIGNIFICANCE OF THE CEREBRAL CORTICAL LAYERS (Neopallium).

General Remarks (p. 98). *Micrometric Measurements of the Cortex of the Mole* (p. 102). *Inferences* (p. 107). *Conclusions as to the Functional Significance of the Supra-Granular and Infra-Granular Cortical Layers* (p. 109).

FURTHER CONCLUSIONS AS TO THE FUNCTIONAL SIGNIFICANCE OF THE CORTICAL AREAS IN THE INSECTIVORA (p. 111).

* The term neopallium is employed throughout in the sense suggested by Elliot Smith to indicate the variable area intercalated between the "basal pallium," or pyriform lobe and the marginal pallium, or hippocampus.

BRAINS EXAMINED AND METHODS OF STUDY.

The brains examined of the animals belonging to the order Insectivora were :—

- I. The Mole (*Talpa europæa*).
- II. The Shrew (*Sorex vulgaris*).
- III. The Hedgehog (*Erinaceus europæus*).

The brains, as a routine practice, were hardened in commercial formalin diluted to 5 per cent. Although this is not an ideal fixative fluid its use was necessary, because in the instances of the more bulky brains employed in this investigation in its wider sense, it appears to be the most generally useful one we possess. Moreover, many of the brains came from long distances, and the means required for the more elaborate methods of fixation were not always at the disposal of those who kindly sent them. Hence, formalin was employed as the hardening agent for all the brains—small and large—so as to ensure, as far as possible, uniformity of results, particularly with reference to the depth of the cortical layers.

The several hemispheres, after being carefully drawn, were divided into blocks—different hemispheres of the same species of animal being used for obtaining blocks (transverse, longitudinal and diagonal), as nearly as possible at right angles to the course of the cortical lamination. The blocks, imbedded in paraffin, were cut entirely through by means of the Cambridge rocking microtome, into sections of the thickness of 10 μ . At least every tenth section was mounted—in some regions practically every section—and stained by one or other modification of the Nissl method. Polychrome blue was the dye most relied upon because of the definition it gives and its relative permanency; other methylene dyes and Heidenhain's iron alum-hæmatoxylin method were frequently employed; some preparations have also been made after the method of Cox. Sections have thus been obtained in every possible "practical" direction. Great care was taken to avoid obliquity; entire avoidance of this in every part of these small hemispheres is often an impossibility, but it is of the greatest importance that no oblique portion of a section should be

made use of in estimating the relative depths of *all* the different cortical layers. Reliance placed upon serial sections of one of these small brains made, say, from pole to pole, without previously dividing it into blocks as nearly as possible at right angles to the course of the lamination, would lead to nothing but the most misleading conclusions as to the depths of the cortical layers.

In the study of the primary cortical layers, for reasons which will become obvious, sections stained for nerve cells only have been employed. Although it is not intended to neglect the fibre architecture of the cortex in animals higher in the scale than in the Insectivora, in the latter the fibre systems of the cortex (as seen in celloidin imbedded preparations stained for nerve fibres), especially those of the upper part, stain very feebly, and appear to be relatively very poorly developed. Such preparations have proved of little assistance in the study of the cortex and even in the delimitation of the cortical areas.

In constructing the maps of the cortical areas, some of which, in a diagrammatic form, are here reproduced, outlines of the cortex, &c., shown in the various sections, have been made by means of the Edinger drawing apparatus, and upon these outline drawings the different types of cortical lamination have been marked. The cerebral hemispheres, of course, of the Hedgehog, Mole and Shrew, are very small (the latter especially), and the orientation difficulties, when dealing with minute blocks from such small brains, are very great, so that it is not pretended that the maps obtained of the cortical areas are anything more than probably approximately correct.

As part of the method of study throughout the entire investigation, the natural habits of the animals examined and their educability, as far as facts relating to the latter are available, have been considered when attempting to correlate structure and function.

MACROSCOPIC APPEARANCES.

A brief general description will first be given of the brains of the three animals included in this series. Most

of the points alluded to in this description, if not all, have been noticed by previous workers. All are macroscopically almost smooth highly macrosmatic brains. That of the Hedgehog is, according to Elliot Smith, one of the simplest and most generalised of mammalian brains. "It closely resembles the brain of the Polyprodon Marsupials (and especially *Perameles*) in all points, except the arrangement of the cerebral commissures and the hippocampus." The Hedgehog, like all Eutheria, possesses a genuine although small corpus callosum, whilst the Marsupials have none in the true sense.

In the brains of the three Insectivores examined, owing to the large development of the olfactory apparatus and the smallness of the neopallium, the well defined rhinal fissure appears in the lateral view of the hemisphere to be placed very high up, especially is this so in the Hedgehog, because of the narrowness and greater depth of the brain as compared with that of the Mole and Shrew. Hence, viewing the brain from the dorsal aspect, the rhinal fissure can be seen in practically its entire length. In none of the brains however (although the distance of its extension varies somewhat in individual brains belonging to animals of the same species), does the rhinal fissure extend the whole length of the hemisphere, so that around the posterior end of this fissure the pyriform lobe and the neopallium *appear* to become continuous.

In the Hedgehog, the anterior portion of the dorso-lateral surface, at about the junction of the first and second quarter presents a short but fairly distinct furrow, the transverse orbital or presylvian as in *Perameles*. This shallow furrow becomes converted into a deep sulcus in the nearly related and larger *Gymnura* (Elliot Smith). In the brain of a Virginian opossum (*Didelphys marsupialis*), kindly sent to the writer by Dr. Koch, there is in a position similar to that of the same named furrow in the Hedgehog a very distinct and curved presylvian sulcus in each hemisphere, almost as well defined on both sides as is the rhinal fissure, which it appears to join. The Shrew shows no trace of this presylvian furrow. Out of twenty brains of

the Mole examined by the writer, some only exhibited a macroscopic indication of an extremely shallow furrow in about the anterior quarter of the hemisphere, which probably corresponds to the presylvian. This furrow is distinctly seen on microscopic examination.

No trace could be found in the brains of the Hedgehog, examined by the writer, of the shallow antero-posterior fissure described by Gustav Mann, and which, he thinks, corresponds to the lateral fissure.

The Hedgehog presents more or less half way along the rhinal fissure a very indefinite short depression, which may represent a rudimentary sylvian fossa, but this is not found in the Mole and Shrew.

The brain of the Mole especially is relatively broader and much less deep, *i.e.*, appears more flattened than that of the Hedgehog. Reference will be afterwards made to the probable significance of the shape of the hemisphere in relation to the absolute depth of the cerebral cortex.

The optic nerves in the Mole and Shrew are reduced to the size of small threads; in the Hedgehog these nerves are relatively distinctly larger. In all three animals the fifth nerve is large.

FURROWS SEEN ON MICROSCOPIC EXAMINATION.

It may be conveniently stated here that certain other furrows have been found on microscopic examination.

The most distinct of these are seen in the Mole. In addition to the oblique presylvian already alluded to, two inconstant slight depressions of the cortex may be observed in some specimens of this animal's brain running more or less longitudinally (see fig. 1, p. 65, and photomicrographs), the one, on the whole the more constant, about a quarter of the distance between the dorso-mesial margin and the rhinal fissure; the other (much the shorter) nearer the rhinal fissure. The more internal of these furrows, towards its posterior third, becomes broader with an inclination outwards. This portion of the furrow is more constant than the remainder, and probably corresponds to the fissure

described in the Mole's brain by Hermanides and Köppen. It is distinctly seen in longitudinal sections of the region.

It is possible that these furrows, in at least part of their course, are due to local shrinkings of the cortex in the process of hardening. If this is the case they should be as prominent in the brains of the Hedgehog and Shrew as in the Mole, but in the brains of the former animals they were either absent or extremely slight in the specimens examined by the writer. Moreover, the constancy of their position when present, and the fact that the cortical layers in their neighbourhood show a corresponding and regular dip, would indicate that they are genuine foldings of the cortex. In addition to these furrows several vascular grooves were found characterised by a slight dipping of the molecular layer only. The furrows differ in different hemispheres, not as to situation, but as to depth and distinctness—in many sections one or other practically disappears. In the brain from which the photomicrograph showing the longitudinal furrow were taken the more mesial of the two was more distinct in one hemisphere than in the other; the more external was more distinct in the opposite hemisphere. The diagram (fig. 1) is a composite one. It should also be stated that in some of the hemispheres of the Mole examined traces of these furrows, or, indeed, of any others, excepting, of course, the rhinal and hippocampal, were so slight that the furrows might be considered to be practically absent. Whilst, therefore, not much stress can be laid upon the existence of these furrows, yet, as they were distinctly present in at least two of the hemispheres examined, and for the reasons given above believed in these to be genuine furrows, some little interest attaches to their presence. In the Colugo (*Galeopithecus volans*) an arboreal highly macrosomatic mammal nearly related to the true Insectivores, there is, according to Elliot Smith, a definite longitudinal sulcus almost as long as the hemisphere with a slight concavity towards the mesial plane. This is considered by the observer just mentioned to represent either the suprasylvian or lateral sulcus, or the conjoint suprasylvian and coronal. The somewhat curved longitudinal

microscopic furrows alluded to in the brain of the Mole would appear to represent dim and inconstant foreshadowings in a lowly mammal of the coronal and suprasylvian sulci of higher forms.

The relation which the various furrows described bear to the different modifications of cortical lamination which have been mapped out will be sufficiently gathered from reference to the diagram (fig. 1, p. 65).

THE ARCHIPALLIUM.

For the reasons stated (p. 51) it is not proposed in the present paper to describe the microscopic appearances of the cortex of the pyriform lobe or the hippocampus. It will therefore be sufficient to say that the abrupt change in lamination, familiar to all comparative histologists, which occurs at the rhinal fissure as one passes from neopallium to pyriform lobe, is well marked in the brains of the Insectivores examined. It has been mentioned that the rhinal fissure does not extend macroscopically to the posterior pole of the hemisphere, and that around the hinder end of this fissure the neopallium and pyriform lobe appears to be continuous. When the microscopic limits of the fissure are reached the change in lamination from neopallium to characteristic basal pallium is still very obvious, and there is no difficulty in mapping the extent of the former. The relations of the basal pallium to the neopallium are sufficiently indicated in the diagrams of the cortical areas in the Mole (fig. 1, &c.), and the differences at the posterior aspect of the brain between the Hedgehog and Mole—differences doubtless due largely to shape of hemisphere—are shown in diagrams (figs. 5 and 6, p. 84).

It is worth noting perhaps, that the structure of the archipallium from the point of view of cell form is thoroughly in keeping with its older phylogenetic origin. Its nerve cells are well organised and developed, those of the pyriform lobe for example, present a striking contrast to the more or less embryonic looking cells of the neighbouring "lateral area of undifferentiated cortex," especially those in the posterior part of the latter area.

As will be afterwards pointed out the neopallium in its earliest attempts at evolution of structure, which later become of any considerable functional value appears to follow the plan which has long previously been laid down, and has become fixed in the hippocampus.

THE NEOPALLIUM.

General Remarks on Lamination.

Before describing the cortical areas it is necessary to give a brief account of the data upon which the distinctions drawn between the various regions have been based, and a definition of the terms used in the description of their lamination.

The classification of the cortical layers adopted by the writer in the course of his investigation of the cerebral cortex in the mammalian series, is that introduced by Bolton. The latter considers that the human cerebral cortex is constructed upon a five layered type, viz.: (1) molecular; (2) pyramidal; (3) granular; (4) inner line of Baillarger; (5) polymorphic. Of these only three are primarily cell layers, the pyramidal, granular and polymorphic; layers 1 and 4 being primarily fibre or cell-process layers, although containing nerve-cells—the cells of Cajal in layer 1, and the Betz cells (“psycho-motor” region) or solitary cells of Meynert (other regions) in layer 4. The above system of classification bears some superficial resemblance to others, especially perhaps the older ones of Meynert and of Betz, but it differs from these in being founded upon a developmental basis, and not merely upon adult cell form.

The outstanding features of this scheme are as follows:

(1) The recognition of the granular layer as separating the true pyramidal layer above from the more or less pyramid *shaped* cells, which are found below this layer, for the cells of layer iv. are not “pyramidal” cells at all, the Betz cells in the psycho-motor area constituting “the origin of the important tract for skilled voluntary movement,” whilst the solitary cells of Meynert in other regions “probably possess a somewhat analogous function.”

(2) The consideration of the pyramidal layer as forming *one* layer developmentally and functionally.

As any attempt to discuss the merits of the very numerous systems of classification of the cortical lamination which have been described by various observers would serve no valuable purpose, the writer will content himself by stating that in the course of his work he has found the above classification to form a most useful and exact basis for general purposes. Various details as affecting the cortex of different mammals, or of different regions in the same mammal can be readily added, without necessarily assuming that the lamination in these animals or in these regions is *essentially* different. The classification, moreover, apart from its developmental and histological soundness has the advantage of furnishing a valuable clue when one endeavours to compute with some exactness the functional significance of the cortical layers.

When dealing with the mammalian cortex generally, one or two further explanations are necessary. The term "granule" is used in a wide generic sense. Most of the cell constituents of the so-called "granular layer," may actually appear under a low magnification to be granules, being cells with a relatively very large nucleus, little cytoplasm and indefinite processes, or they may take the form of angular, quadrilateral, stellate, or even small pyramidal cells, or finally a mixture of these elements. In some regions of the cortex in certain animals these "granular" elements may be scattered and comparatively few in number, so that one may be tempted to consider that the granular layer, as a layer, is non-existent; yet the recognition of these elements, however few and however disguised their form may be (*i.e.*, the granular layer as a primary developmental lamina) is in the experience of the writer invariably possible and is always advisable, for such recognition provides the means by which the lower limit of the later developed true pyramidal layer may be determined, or at least by which this layer may be separated from the subjacent layers.

It should also be added that owing to the difficulty experienced in the cortex of some animals of accurately

separating the 4th and 5th layers, the writer prefers at the present time to speak of those layers together as "infra-granular." Further reference will be made to this point. It is also proposed, in order chiefly to avoid confusion as to what is meant by the term "pyramidal," to speak of this layer (layer ii.) as the "supra-granular" layer, this being understood to correspond to the true pyramidal layer only, and not, of course, to include the small nervous elements which may be found in the molecular layer.

[As considerable differences exist in the use of the term "line of Baillarger" by various writers a brief account may here be given of the reasons which appear to exist for these differences. Gennari, and Vicq d'Azyr each discovered a *macroscopic* transverse strie in the human occipital cortex. Baillarger described two striæ in the common type of cerebral cortex—the "strie externe" and the "strie interne." The names of these three observers have been applied somewhat indifferently by later workers to certain transverse bands of fibres (*microscopic*) existing at different levels in various parts of the cortex as seen in sections stained for the display of nerve fibres.

In the developing human cortex cerebri as shown by Bolton a pale band very early appears which separates the granular layer above from the polymorphic layer below. This pale band, which thus lies *below* the granular layer is found in every region of the neopallium and occupies the site of what afterwards becomes the *inner* line of Baillarger. It is a fundamental cortical layer just as is the molecular or superficial layer. In it and in its neighbourhood is developed in the adult human cortex an extraordinary wealth of cross and other fibres so that the exact limits of the layer are much obscured in an ordinary specimen stained by some "Weigert-Pal" process for the display of nerve fibres only.

In certain parts of the adult human cortex however, *e.g.*, in the prefrontal and in portions at least of the temporal and parietal regions, there exists another more or less definite transverse band of fibres situated above the inner line of Baillarger—indeed placed mostly at and about the *upper* limit of the granular layer. This upper band of transverse fibres probably corresponds to the "strie externe" described by Baillarger and appears to be homonymous with the line of Gennari in the calcarine region although it does not constitute a line of Gennari in the sense of a fibre line in the midst of a duplicated layer of granules, for only in the calcarine region (*i.e.*, "visuo-sensory area" of Bolton), and in this only, so far as the writer's observations have gone in the Primates,

is a double layer of granules found with a definite fibre band (line of Gennari) between them.

This accessory line of Baillarger (*strie externe*) does not therefore appear to be a fundamental cortical layer as is the inner line (*strie interne*), but rather like some other cross bands of fibres which have received special names, *e.g.*, the stripe of Kaes, it is merely a band of fibres developed in various regions in connection with the specialisation of certain cells belonging to a fundamental cortical layer. In the writer's opinion the names and numbers of the cortical *layers* should be restricted to those which are of fundamental origin, for the laying down of a *lamination* is a very different thing from the specialisation of certain cell elements of a true cortical layer and the development of nerve fibres in relation to these. Incidentally it may be mentioned that the position as above indicated of the outer line of Baillarger when this is present, *viz.*, above the granular layer, suggests that of the duplicated layer of granules in the "visuo-sensory" cortex the lower layer is the original one, and that in the Primate visuo-sensory area it is the upper layer of granules which is added.

Owing to the writer's adoption for purposes of convenience in this research of the designations "supra-" and "infra-granular" portions of cortex the term inner line of Baillarger is not hereafter used.]

FUNCTIONAL SIGNIFICANCE OF THE CEREBRAL CORTICAL LAYERS.

Bolton,* as the result of his studies of the development of the human cortical layers and of their depth in the adult normal individual as well as in various degrees of amentia and dementia, has come to the following conclusions as to the functions of the three primary cell layers:—

(1) The pyramidal layer is the last cell layer of the cortex to develop during the process of lamination, and it is also the first to undergo retrogression in dementia. In aments its depth varies with the mental power of the individual, and its amount of retrogression in dementia with the degree of dementia. It therefore "suberves the psychic or associational functions of the cerebrum."

(2) The granular layer is developed before the pyramidal. It probably "suberves the reception or immediate trans-

* ARCHIVES OF NEUROLOGY, vol. ii., 1903.

formation of afferent impressions, whether from the sense organs or from other parts of the cerebrum."

(3) The fifth or polymorphic layer is the first layer to be differentiated, and it is the last to fail in the retrogression of dementia. A decrease in this layer exists in extreme aments—whether normal infants or idiots—and in demented who are unable to carry on the ordinary animal functions, such as attending to their own wants. "This layer, therefore, probably subserves these lower voluntary functions of the animal economy."

These statements as to the ontogenic development of the cerebral cortical layers have been confirmed by the writer in the instances of a fourth, a sixth and an eight month human foetus, and the same relative order of development of the layers has been found by him to hold good regarding the cerebral cortex of several foetal and newborn lower mammals. Further, in the cases examined by the writer, of juvenile general paralysis,* with extreme dementia (some were also cases of amentia) the pyramidal layer showed the most marked atrophy or under development of all the cortical layers.

AREAS OF THE NEOPALLIUM AND THEIR LAMINATION.

Under this heading a somewhat detailed account will be given of the Mole because the appearances of the cortex in this animal are very similar to those in the Shrew, and because the cortical lamination is more easy to follow than in the Hedgehog, the arrangements of the cortical nerve cells being more regular and orderly than in the latter. The Mole may therefore be taken as a type, and the differences in cortical structure between this animal and the Shrew and Hedgehog afterwards mentioned.

I. THE MOLE. (*Talpa europæa*.)

(1) DORSO-LATERAL SURFACE OF THE NEOPALLIUM.

This region extending from the inter-hemispherical cleft mesially, to the rhinal fissure and the microscopic continua-

* Ibid.

tion of this backwards and upwards towards the posterior pole laterally, presents two main and very distinct varieties of cortical structure.

(1) *Area 1.*

This occupies a large region extending antero-posteriorly from a short distance behind the anterior pole to about the posterior quarter of the hemisphere, and laterally, from the dorso-mesial margin or close to this anteriorly and overlapping this posteriorly, to about half-way between the dorso-mesial edge and the rhinal fissure, the lateral limits varying somewhat at different points (see fig. 1, p. 65).

As regards its lamination this area presents the following features :—(See photomicrograph, Plate I., 1.)

(1) Molecular layer, containing a few small nerve elements.

(2) Supra-granular (pyramidal) layer, made up of small more or less pyramidal, angular or bicornuate cells, placed two or three deep, with stout processes, irregularly arranged and rather closely packed together ; below these are rather scattered, somewhat larger and more definitely pyramid-shaped cells, often erect but not very regular in arrangement. These latter cells are in places three or four deep, and may be considered to belong to the supra-granular layer.

(3) Granular layer, containing fairly numerous, somewhat scattered, rounded small triangular or quadrilateral cells, which in preparations obtained after the method of Cox show numerous delicate branching processes. These elements do not form such a deep and definite layer as they do in the area next to be described.

(4) Fourth layer, consisting mainly as regards cells of long, rather narrow, pyramid-shaped cells ; erect and chromophilous with extensive apical processes, but with few side or basal processes (even as seen in preparations after the method of Cox), and with no very definite chromatic elements. These have some slight tendency to occur in groups ; they are often four or five deep, are the largest

nerve cells of the neopallium, and are probably the analogues of the Betz cells seen in higher forms. It may be mentioned that these cells appear to have a somewhat simple structure recalling in some respects that of the densely staining long pyramid-shaped elements of the hippocampus, pyriform lobe and gyrus fornicatus in higher forms.

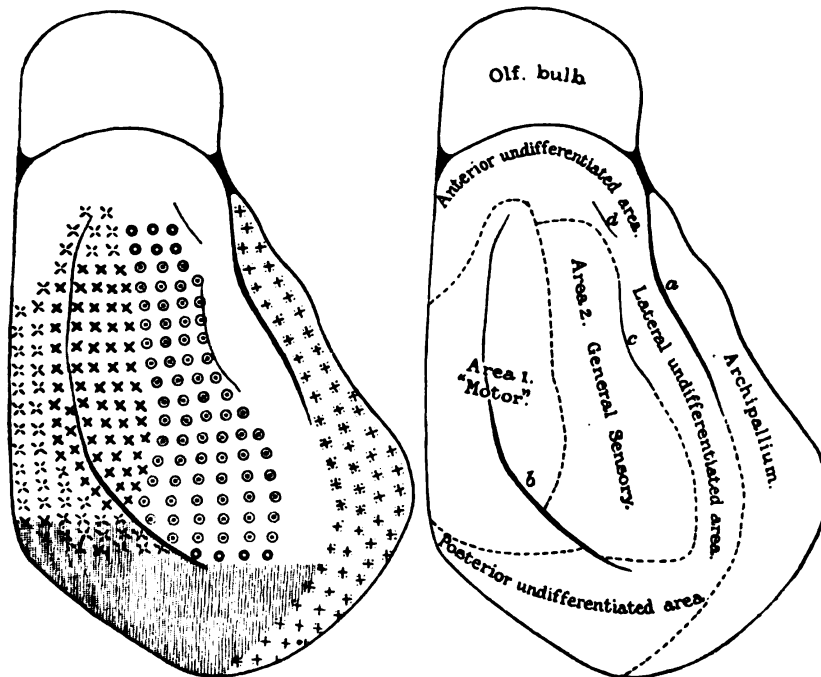


FIG. 1.—DORSO-LATERAL VIEW OF THE RIGHT HEMISPHERE OF THE MOLE.

Left-hand figure: x Area 1, "Motor"; x the same, but less characteristic; o Area 2, General Sensory; o the same, but less characteristic; ≡ Archipallium.

The anterior, lateral, and posterior areas of undifferentiated cortex are left blank excepting the portion of neopallium represented as shaded, which is thinner than the remainder.

Right-hand figure: a, rhinal fissure; b, c, and d, probable representatives respectively of the corono-lateral, supra sylvian, and presylvian sulci; b, c, and d, vary much in individual distinctness in different hemispheres. The figure is a composite one.

(5) Polymorphic layer: this contains various-shaped elements—medium sized pyramids chiefly in the upper part, in the lower part more irregularly shaped cells, whilst in the lowest limits of the layer the cells are more or less

"reclinate" and fusiform in shape. Towards the lower portion of the layer the cells tend to be arranged in rows producing a somewhat stratified appearance of the cortex, whilst in the upper part they penetrate amongst the larger cells of layer iv., and even encroach upon the lower limits of the granular layer. There thus appears to be some intermingling of layers iv. and v., and it is difficult to accurately separate the two; hence these layers together may be conveniently termed "infra-granular" to distinguish them from the "supra-granular" (pyramidal) layer.

Whilst in the anterior, posterior and mesial limits of this area, the appearances are generally similar to those above described, yet (as indicated in fig. 1) the characteristic features in these portions are less marked.

(2) *Area 2. General Sensory.*

This area is narrow in front, but broadens out behind. It occupies an extensive region, lateral to Area 1 and slightly posterior to this, but does not reach as far as the rhinal fissure, being separated from the latter by a zone of undifferentiated cortex (see fig. 1).

As compared with Area 1 the following particulars may be noted regarding the cell lamination of Area 2.

The supra-granular layer is of approximately the same depth, and presents much the same characteristics. The granular layer not only shows an appreciable increase in depth, but its component cell elements, whilst having the same general shape (although, on the whole, they are not so large), are more numerous and more closely crowded together, especially and comparatively in the upper part of the layer. The infra-granular cortex exhibits a considerable increase in depth, chiefly of the polymorphic portion; the cells of layer iv., whilst preserving the same general features as in Area 1, are, generally speaking, smaller, and are more distributed; at most, they are only two or three deep, and occasionally they are even solitary.

Owing to these histological differences between Areas 1 and 2, especially in the matter of the granular layer, the

increase in depth of which, as one passes lateralwards, is sudden and abrupt, the two areas can be readily separated the one from the other. Laterally, also, the limits of Area 2 can be fairly easily made out, but anteriorly and posteriorly the features characteristic of the area (as in the case of Area 1) only gradually disappear.

It is concluded that, on account of its possession of a relatively greater developed granular layer, Area 2 is primarily sensory in function, and, further, that it is probably analogous to the kinæsthetic area of higher forms.

(3) *Areas of Undifferentiated Cortex.*

In the lateral, antero-mesial and postero-mesial portions of the neopallium are three fields of moderate size, the limits of which are sufficiently indicated in figs. 1 and 3.

Whilst supra- and infra-granular portions of cortex are found, the lamination of these areas not only presents no definitely specialised features, but the individual cell elements in the several layers are relatively poorly developed, many being of a more or less embryonic character (compare photomicrographs 1 and 4, Plates I. and II.). Certain slight differences, which will be presently mentioned, occur in the three fields.

(a) *Lateral area of undifferentiated cortex and (?) eighth nerve area.*—Immediately above the rhinal fissure, between this and Area 2, is a somewhat oval-shaped region, coincident with all but the more anterior portion of the rhinal fissure. A faint, somewhat curved, longitudinal furrow (? supra-sylvian) seems sometimes to separate this region mesially from Area 2; the furrow, however, is inconstant (see fig. 1 and photomicrograph, Plate I., 2).

The interpretation of this portion of the "lateral area" presents some difficulties. At first sight, it appears to possess considerable cell wealth, but this is no doubt partly due to the region being in proximity to the rhinal fissure, thus forming what would correspond to the apex of a convolution. In its structure this region differs from Area 2 chiefly in its diminished granular cortex, in the

increased depth of the infra-granular cortex (owing to the region forming practically part of an apex of a convolution), and in the absence of the largest pyramid shaped elements in the latter. The individual cells generally are also less well developed than in Area 2.

Originally the writer was inclined to look upon this portion of the lateral area as sensory in function and by analogy to credit it with the representation of the cortical distribution of the 8th nerve. This view is supported by Campbell's statement that a small field investing the so-called fissure of Sylvius in lower mammals (the Cat, Dog and Pig), appears to be the analogue of the audito-sensory area in the human subject, and the position in the Mole's cortex of the region in question, viz., in what would correspond to the ecto-sylvian region had the animal a pseudo-sylvian fossa. Dr. Bolton's accurate micrometric measurements of the cortical layers in this region (see p. 102), however, show that the appearances of cell wealth in the granular layer are illusive, and that this layer in this region is actually less in depth than it is in Area 1. If layers II. and III. are taken together in order to eliminate any personal equation which might arise concerning the separation of these layers, it is found that their conjoint depth is practically the same as that of the same layers in Area 1. In view of these facts, it seems probable that the region in question is not a characteristically sensory field at all, and that it is more correct to regard it as forming a portion of the lateral area of histologically undifferentiated cortex.

From such observations as the writer has been able to collect with reference to the Mole, it would appear that this animal makes comparatively little use of the sense of hearing, but it seems that vibratory impulses are readily appreciated, and it is not unlikely that the capacity for appreciation of such impulses, together with other 8th nerve impressions, is of considerable importance to animals of underground or nocturnal habits. Whether this sense of vibration is chiefly dependent upon 8th nerve impressions, it is difficult to say. The writer has, therefore, been unsuccessful in his attempts to delimit an area which can be

said to possess definite sensory characteristics in the region of neopallium, in which, by analogy, one would expect to find the 8th nerve represented, viz., in the homologue of the ecto-sylvian region. At the same time, he thinks that the anterior portion, roughly speaking, of the "lateral area" in the Mole is somewhat better developed than the posterior, and, as compared with the latter, possesses some indefinite sensory features. It may be that 8th nerve impressions have some dim representation in this region, but that such impressions have not been of sufficient importance to the survival of these animals to warrant the development or persistence of a very definite and specialised *cortical* representation.*

(b) *Antero-mesial area of undifferentiated cortex.*—This occupies the neighbourhood of the frontal pole and extends to the mesial aspect. Not only does the lamination here present no special features, but the individual cells are relatively even less well developed than in the other two undifferentiated areas.

(c) *Postero-mesial area of undifferentiated cortex.*—Behind Areas 1 and 2, extending to the occipital pole and overlapping to the mesial surface, is a region of relatively thin cortex. In longitudinal or angular sections of the hemisphere the cortex is observed to become somewhat gradually less deep in about the posterior quarter to one-third of the hemisphere. The diminution in depth gives rise in such sections to the appearance of a furrow, presumably that described as "furrow b" by Hermanides and Köppen. There certainly does appear to be a genuine furrow in this region, which seems, from a study of sections taken in various directions, to be a continuation of the faint internal longitudinal furrow previously mentioned,

* In a preliminary communication on the subject of this paper (Proceedings of the Royal Society, B. Vol. 77, July 28, 1905), the writer having failed to locate a definite sensory area concerned with the cortical distribution of the 8th nerve, suggested that this area might exist in approximately the outer part of the second quarter of the cortical region designated Area 2. In this case, however, the faint inconstant furrow before referred to could not be regarded as corresponding to the supra-sylvian. What is of more importance is the fact that no criteria were found by means of which Area 2 could be separated into two distinct fields. The explanation above attempted appears to be more in accordance with the facts.

which in this situation becomes deeper and broader and takes a course rather obliquely outwards (see fig. 1). This thinner portion of cortex is observable in sections taken in every possible "practical" direction, and is therefore not due to obliquity of section. In a tranverse section of about the middle of this region the total depth of the cortex is found to be only about two-thirds of that in Areas 1 and 2, and the structure generally is much simpler than in these areas, although the individual cells are, on the whole, better developed than in the antero-mesial area of undifferentiated cortex.

The structure of this area is characteristic. The individual cell elements appear to have a certain independence, and those belonging to the different layers become more or less like one another. This is particularly noticeable in the infra-granular cortex, where the cells are arranged in lines parallel to the surface in a sort of stratified manner. Some tendency to such an arrangement of the cells of the polymorphic layer has already been noted in connection with Area 1, but in the "posterior area" it is even better displayed. The appearance and arrangement of the cells just referred to is somewhat reminiscent of that seen in the cortex of a foetal, or rather in that of a very young mammal.

It should again be observed that there is no sudden transition from Areas 1 and 2 to this posterior region of undifferentiated cortex. There is a gradual fading of the two former into the latter. On the dorsal surface Area 1 mesially preserves its characteristics more or less for a short distance as one passes backwards, as does Area 2 laterally. The supra-granular layer slowly loses some of its features, the larger cells of the infra-granular cortex become smaller and the "stratification" of the polymorphic layer more evident.

(2) ANTERIOR SURFACE.

Occupying almost the whole of the anterior and inferior aspect of the frontal pole is a small area presenting the following characteristics. Superficially is seen a somewhat thin layer of cells, four or five deep, apparently supra-

granular in position (since the granular layer is indefinite) and individually well developed, being bicornuate or small pyramidal and having numerous processes. Below these cells, and curving forwards to join the olfactory bulb, are several rows of fairly large erect pyramid-shaped cells, mixed with which are granular and polymorphic elements. The area is sharply marked off from the relatively poorer and less differentiated cortex behind it, and may constitute a neopallial representation of the olfactory sense. No further reference will be made to this region.

(3) MESIAL SURFACE.

This may be divided into (a) *the anterior straight mesial portion*; (b) *the curved postero-mesial portion* which arches over and round the mesencephalon and hippocampus somewhat in the form of a bow (see fig. 3, p. 73).

(a) *The anterior straight portion* presents in the main three different varieties of cortex, with posteriorly and inferiorly the commencement of the very specialised region shortly to be described.

(1) In about the anterior quarter is an area with poorly developed cells continuous with that on the dorsal surface, and before referred to as the antero-mesial area of undifferentiated cortex.

(2) Behind this and occupying the remainder of the surface not taken up by the overlapping Area 1 and the commencement of the above mentioned very specialised region, is a somewhat indefinite area. Although the component nerve cells of this area are rather less embryonic in type than in the adjoining antero-mesial area of undifferentiated cortex, they are less well developed than in the neighbouring modified motor cortex and postero-mesial specialised region. At the same time the lamination is more confused than in the latter regions, and does not present any specialised features.

(3) Behind and above the last described field is a region joining Area 1 on the dorsal surface, and, like it, exhibiting motor characteristics, although here these characteristics are less pronounced.

(b) *The curved postero-mesial portion.*—Owing to its shape it quickly became apparent that no correct idea of the extent, structure and relations of the postero-mesial region of the cortex could be obtained by confining one's attention to the examination of sagittal and coronal sections of the hemisphere; indeed, because of the necessarily very

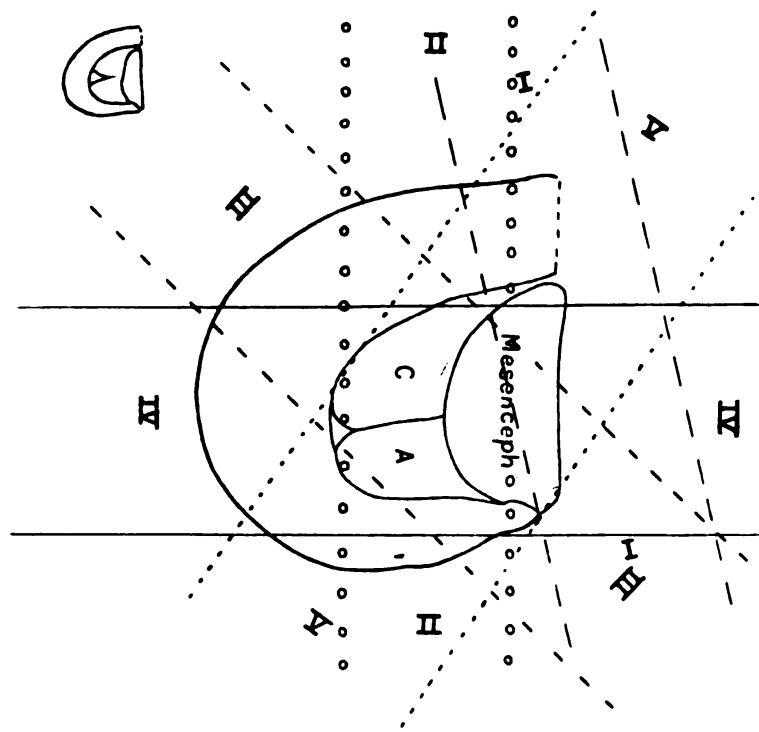


FIG. 2.—Composite diagram of the posterior aspect of the left hemisphere of the Mole, to indicate the position of the blocks from which sections were cut of the postero-mesial region, several hemispheres being used. In the left-hand top corner is a representation of about the actual size of the posterior end of the brain.

oblique manner in which the lamination of many portions of this region would be caught by such sections, the appearances presented by them are fallacious. Accordingly, the writer made an attempt to obtain sections which should correspond as closely as possible to the course of the lamination in this region, by cutting out blocks the positions of which are indicated in fig. 2. Several hemispheres were

used for this purpose, care was taken in removing the blocks to avoid obliquity as far as possible, and the blocks were designed to overlap each other so that no portion of the area to be described, and its relations, should be missed. The blocks were small, and subsequent orientation was a matter of some difficulty. From sections thus obtained, and comparison of these with sagittal and coronal sections,

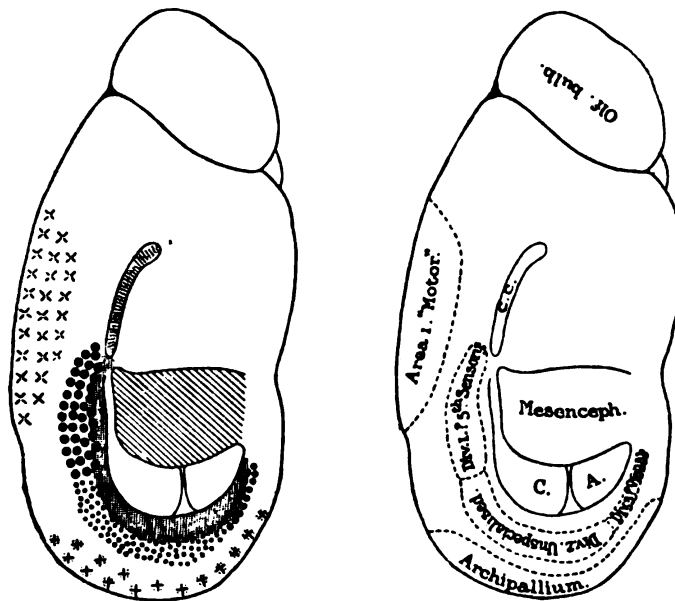


FIG. 3. — POSTERO-MESIAL ASPECT OF THE LEFT HEMISPHERE OF THE MOLE, to illustrate especially the position and relations of the postero-mesial region of cortex characterised by a well marked granular layer. The right-hand figure is explanatory of that on the left.

NOTE.—Division 2 as explained in the text (see footnote p. 77) is better termed “undifferentiated” than “unspecialised.”

a careful study has been made of this region, details concerning which will now be given.

Occupying the posterior and inferior part of the anterior straight and a large part of the curved posterior portion of the mesial cortex is an area of considerable size, which exhibits very specialised features (see fig. 3). It is distinguished chiefly by the presence of a deep and exceedingly definite granular layer, and it appears to be a portion of

neopallium inserted as a curved tongue, broadly speaking, between, on the one hand, the mesial portion of Area 1, and the cortex behind and below this, including archipallium, and on the other the posterior part of the corpus collosum and hippocampus, although separated from the latter by a thin band of different but characteristic cortex.

This area of specialised cortex is apparently continuous along the region indicated, although it varies somewhat in width in different places in its upper and middle parts; towards its lower quarter it appears to narrow considerably and then to slightly broaden out again. A general description of the lamination of this area would be as follows: A deep molecular layer, below which is a prominent and very sharply defined granular layer and a fairly deep infra-granular cortex. Apart from the definite granular layer a very noteworthy feature of this field is the almost total absence of a supra-granular (pyramidal) layer, only occasional larger cells being found, supra-granular in position, which might be said to represent a rudiment of this layer (see Plate II., photos 5, 6, 7).

Whilst in serial sections of this region no absolute break was found in the area of specialised cortex exhibiting the above described characteristics, and whilst, if its principal features only are taken into consideration, it appears to be continuous, yet it presents certain differences in different parts, owing to which the area has been sub-divided into three portions. These, for convenience of description and reference, are named the superior, middle and inferior divisions (Plate II., photos 5, 6 and 7, and fig. 3).

(1) *The superior and anterior division.* — Here the granular layer is very definite, its cellular elements consisting of well formed, small, closely packed, somewhat rounded angular or quadrilateral elements twelve or more deep. The infra-granular cortex contains numerous fairly large, rather broad pyramid shaped cells in its upper part and mixed elements below.

(2) *The middle division* also possesses a fairly deep granular layer, the individual cell elements of which however, are more ill-defined and more embryonic in type than

in the superior division. Another striking feature of this portion is the marked poorness of the infra-granular cortex, the larger pyramid shaped cells being almost absent.

(3) *The inferior division.*—The cortex here is thinner; the granular layer contains many fewer elements, and although these are fairly well formed they are much more scattered and irregular in arrangement than in the superior and middle divisions of the area, so that the boundaries of the lower divisions are less readily determined. The infra-granular elements are also irregularly arranged but rather better developed (though small) than in the middle division.

It should again be mentioned that in none of the three divisions is a definite supra-granular (pyramidal) layer present, the deep molecular layer being succeeded by the granular layer, only a few scattered fairly large cells, supra-granular in position, intervening.

This area of specialised cortex is not confined to the postero-mesial surface entirely, but in its superior and middle divisions especially, encroaches upon the overhanging ventral surface. The lateral limits of the area in the greater part of its extent are exceedingly abrupt and definite: its relations with the cortex coating the remainder of the postero-mesial surface of the hemisphere will be best understood from a glance at figs. 3 and 5. Along the border where it is in relation with the hippocampus it is always separated from the latter structure by a characteristic cortex, composed chiefly of large darkly staining pyramid shaped cells several rows deep. Superiorly and anteriorly it is in relation with the mesial modified motor cortex which overlaps from the dorsal aspect, posterior to this with the postero-mesial area of undifferentiated cortex, and behind and below the latter with the basal pallium, which here comes round from the dorso-lateral and inferior aspects of the hemisphere.

The orientation difficulties which have been encountered in the effort to obtain an accurate idea of the condition of the cortex in the region under consideration will, perhaps, be appreciated by those who have made similar attempts to

study a portion of *cerebral cortex*, which is actually very small in area and is at the same time folded in more than one direction. In spite, however, of these difficulties the writer feels confident that the limits of the area which he has mapped out having the above described specialised features are approximately correct, and, in particular, that it does not extend on to the dorsal aspect of the hemisphere. From the point of view of comparative histology, it is of some importance that the latter fact, viz., that the area in question is limited to the mesial and a small part of the ventral aspects, should be emphasised, for in some mammals higher in the scale than the Insectivora, part of what appears to be the analogue of this area does extend round the occipital pole and on to the dorsal aspect of the hemisphere.

Whilst the writer believes that his map of this specialised area, as a whole, is approximately correct, he thinks that there is more room for difference of opinion regarding his attempt to further sub-divide it, and especially, perhaps, regarding the relative size of the separated portions.

The distinctions which he has endeavoured to draw between the three divisions of the area cannot be readily followed excepting by a careful study of a large number of serial sections. The differences between the superior and middle divisions are easily made out, if sections from about the middle of each of these portions are examined, but there is no abrupt change from the one portion to the other, the two shading almost insensibly to one another. The inferior division in the Mole is a somewhat indefinite field, and it was only by careful comparison of this with the corresponding area in the Shrew, and especially in the Hedgehog, that it was decided that it formed a portion of the neopallium at all.

The above facts may be briefly summarised as follows:—Occupying the posterior and inferior part of the anterior straight mesial, and a large part of the curved postero-mesial (extending slightly also on to the ventral), aspect of the hemisphere is an area of specialised cortex, characterised by a very prominent granular layer and by the practical

absence of a supra-granular layer. Owing to certain histological features a further subdivision of this area may be made. The superior and inferior divisions are the more highly differentiated, and are separated by a middle field having the same specialised features, but which is comparatively undifferentiated or undeveloped, that is to say, the individual cell elements it contains retain a more or less embryonic character. Of the superior and inferior divisions the former is the larger and more histologically distinct field.*

On account of the possession by this specialised area of an exceedingly prominent granular layer, it is concluded that it is primarily sensory in function, but the discussion as to its exact function will be postponed until the homologous area in the Shrew and Hedgehog have been described.

The structure of this specialised area—consisting essentially as it does of a prominent granular layer and of an infra-granular portion of cortex—is reminiscent of that of the hippocampus. This suggests the idea that in the lowest grade of its structure, which is of real functional value, the neopallium follows in its architecture that of the hippocampus, an architecture which is of older phylogenetic origin and which has become, in the latter situation, fixed.

II. THE SHREW (*Sorex vulgaris*).

The structure of the cerebral cortex in this animal and the plan of the cortical areas are so similar to those seen in the Mole that only a brief reference to one or two points is necessary. The arrangement of the cortical layers in the Shrew is very regular and orderly, and the distinctions between the different regions are for the most part readily made out.

Microscopic furrows.—These are less distinct than in the Mole. There were traces of the presylvian, but only

* In the preliminary communication on this subject (*loc. cit.*) the middle division (2) of this field was referred to as "unspecialised." It seems more correct to regard it as specialised, but comparatively to the superior and inferior division as "undifferentiated."

one longitudinal furrow—and this apparently the internal one (as compared with the Mole)—was faintly indicated in (some sections only of) the hemispheres examined. “Furrow *b*” was also less distinct than in the Mole.

Cortical areas.—Areas 1 and 2 are relatively of about the same size as in the Mole and present much the same distinguishing features, especially in the matter of the granular layer. This layer is thicker and more definite in Area 2 than in Area 1; the infra-granular cortex, however, does not show the same gross differences in the two areas that were seen in the Mole; in the Shrew almost as numerous and as large pyramid shaped cells are found in the infra-granular cortex in the greater part of Area 2 as are seen in Area 1, these cells forming a more prominent feature of Area 2 than they do of the corresponding area in the Mole (Plate III., photos 9 and 10).

The *areas of undifferentiated cortex* are perhaps relatively rather smaller than in the Mole—the “posterior area (behind Areas 1 and 2) is very simple in character, and its cortex is considerably thinner than that of Areas 1 and 2; indeed, as it shelves laterally towards the archipallium it becomes extremely thin.

The postero-mesial area of specialised cortex.—Owing to the very small size of the hemisphere the writer has not yet been able to obtain a complete set of satisfactory serial sections of this region in the Shrew. So far as can be judged, it presents features very similar to those seen in the Mole. The area seems to be of about the same relative size, and to be divisible in the same manner as in the latter. The granular layer, however, in the superior and middle divisions, whilst being extremely distinct, is rather less deep, and the cellular elements composing it are somewhat smaller and more rounded than in the Mole. The inferior division would appear to be rather better developed than in the latter, and its lamination to be more regular.

III. THE HEDGEHOG (*Erinaceus europæus*).

The brain of this animal differs in shape from that of the Mole and Shrew, especially the former, in that it is

relatively narrower and deeper. This fact probably has some bearing upon the actual depth of the cortex and upon the relative depths of the different layers.

The fissures and furrows.—With the exception of the rhinal and hippocampal fissures, and some indication of a presylvian furrow and a sylvian fossa, no macroscopic furrows are seen, and the hemispheres examined by the writer were microscopically also almost smooth; only occasional traces of the faint furrows described in the Mole were found, and these had more the appearances of vascular grooves.

The Structure of the Neopallium—General Remarks.

The microscopic appearances of the neopallium in the Hedgehog seem at first sight to present great differences from those seen in the Mole and Shrew. This is owing chiefly to the very disorderly arrangement of the nerve cells, to their complexity, and to the disguised form of the elements of the "granular" layer. These differences are accentuated by the narrowness laterally in the Hedgehog of the neopallium, which is so moulded that it forms what corresponds to the broad and rounded apex of a convolution (see fig. 10, p. 100). If, however, a transverse section of the dorsal cortex, about midway between the anterior and posterior pole of the hemisphere, be examined the following particulars may be noted. Disregarding the cortex of the rounded mesial edge, where the lamination is not so characteristic, and commencing at the comparatively flat surface immediately external to this, the lamination may be found to be made up as follows (Plate III., photo 8):—

(1) A deep molecular layer containing few cellular elements, these being mostly small with an occasional large cell somewhat similar to those in the subjacent layer.

(2) Below this is a layer of cells of varying depth. In the upper part of this layer the cells are bicornuate, angular or polygonal, and are rather crowded together, often some four or five deep and extremely irregular in arrangement;

in the lower part they are more scattered, more erect and regularly placed, and are also more definitely pyramidal in shape. These elements then constitute the supra-granular cell layer, and although the latter resembles in its general features the corresponding layer in the Mole and Shrew, yet it differs from that in the two last-named animals in its extreme irregularity and variability in depth. In places it appears almost to stop (see photo), the constituent cells being only two or three deep; then immediately afterwards there is a sudden increase in depth to perhaps eight or nine cells. Practically every cell of this layer is extremely well developed; stains darkly, has sharply defined incurved sides and numerous well formed branching processes—an appearance very different from that presented by the paler, more globular cell with poor processes characteristic of this layer in the mesial undifferentiated cortex at this level (see photo 16).

(3) Subjacent to the supra-granular layer is a somewhat clearer space containing small, scattered and irregularly arranged cells, angular, quadrilateral or even small pyramidal in shape, amongst which are larger cells of varying form and size. This is believed to represent the "granular" layer, but its limits cannot be very exactly defined.

(4) and (5) The infra-granular portion of the cortex contains in its upper part (layer iv.) fairly numerous and fairly large more or less pyramid shaped elements, some of which encroach upon the granular layer. Many of these cells are long, narrow, uniformly darkly staining pyramids; others are more globose, and generally paler, but contain small chromophilic bodies. One or other of these sets of elements, and possibly both, no doubt correspond to the large cells of layer iv. (analogues of Betz cells) in the Mole and Shrew, but they are relatively less numerous, and lack the regularity of arrangement seen in the latter animals. Below these cells is again a somewhat clearer space, subjacent to which, and corresponding to layer v. (polymorphic), is a zone of cells of almost all shapes and of nearly all sizes, none, however, being quite so large as are the largest cells in the upper portion of the infra-granular cortex.



The Hedgehog possesses, on, roughly speaking, the postero-mesial aspect of the hemisphere, an area of highly specialised neopallium, corresponding to that described in the Mole. An examination of this suggests that the interpretation given above of the lamination of the Hedgehog's cortex generally is correct. Although, as will be afterwards pointed out, this specialised cortex shows in its structure certain differences in detail, yet it presents general features similar to those found in the Mole and Shrew. Here in the Hedgehog there are no cells at all which, even under a low magnification, have a "granular" appearance, the shape of the elements of the undoubted "granular" layer being rather distinctly small pyramidal or angular, like that, indeed, of many of the elements of the layer which has been designated the "granular" in the region of dorsal cortex above described (see Plate IV., photo 11). This appearance affords a useful clue to the interpretation of the lamination of the general neopallium in the Hedgehog, for, although it is admitted that the granular layer in the cortex of this animal is not so definite as it is in that of the Mole and Shrew, yet, without this clue to its interpretation, one might be inclined to think that the elements of the "granular layer" are absent.

Areas of the Neopallium.

(1) *Dorso-lateral surface.*—*Areas 1 and 2.* Taking the above description of the lamination as a basis, it is found that cortex, with these characteristics, occupies the greater portion of the dorsal aspect of the hemisphere, extending (1) longitudinally from a short distance behind the frontal pole to just within the posterior quarter of the hemisphere; and (2) laterally from, at or near the mesial edge anteriorly, and overlapping this posteriorly, to within a short distance of the rhinal fissure, being separated from the latter by a zone of undifferentiated cortex.

This field, then, occupies the same relative position, and is of about the same relative size as are areas 1 and 2 taken together in the Mole. When, however, one looks for differences in this large field which would enable one to

divide it into areas 1 and 2, as was done in the case of the Mole, these differences are not obvious. The granular layer may be somewhat more definite in the outer part of the field than in the inner, and this portion also may show more uniformity in the size of the elements of the upper portion of the infra-granular cortex, with rather fewer of the large pale cells of the Betz type. If these distinctions could be regarded as sufficiently definite, then this field could be divided, as in the Mole, into area 1 (motor), and area 2 (general sensory), and the relative size of these two areas would be about the same as in the Mole. It is feared, however, that these distinctions are somewhat artificial, and that therefore it is perhaps more correct to regard this field as being a general "sensori-motor" area, without such complete differentiation of structure as is seen in the Mole, and, to a less degree, in the Shrew.

Laterally the boundary of this large field is fairly sharp, but towards the anterior, mesial and posterior borders its structure, whilst preserving the same general features, becomes less characteristic and the cortex gradually merges into that typical of the areas of undifferentiated cortex.

(2) *Areas of undifferentiated cortex.*—In the lateral antero-mesial and postero-mesial regions of the neopallium, areas of undifferentiated cortex can be distinguished—areas the lamination of which presents no definitely specialised features, and the individual cell elements in the different layers of which retain a more or less embryonic character, in striking contrast to the well developed cells in the area above described. These areas of unspecialised and undifferentiated cortex are similar in relative position and extent to those found in the Mole.

Lateral area.—As in the Mole, the anterior portion, roughly speaking, of this area is somewhat better developed than the posterior, and perhaps as compared with the latter may be said to possess some indefinite sensory features which by analogy one may perhaps infer are concerned with the cortical distribution of the eighth nerve.

Postero-mesial area.—Behind the sensori-motor region the cortex gradually loses its special features and shades

into the posterior area of undifferentiated cortex, which becomes less deep, particularly in its outer part. The structure of this area is much simpler than is that of the cortex in the sensori-motor region, and the "stratification" of the cell elements, especially those of the lower part of the infragranular cortex, is very evident.

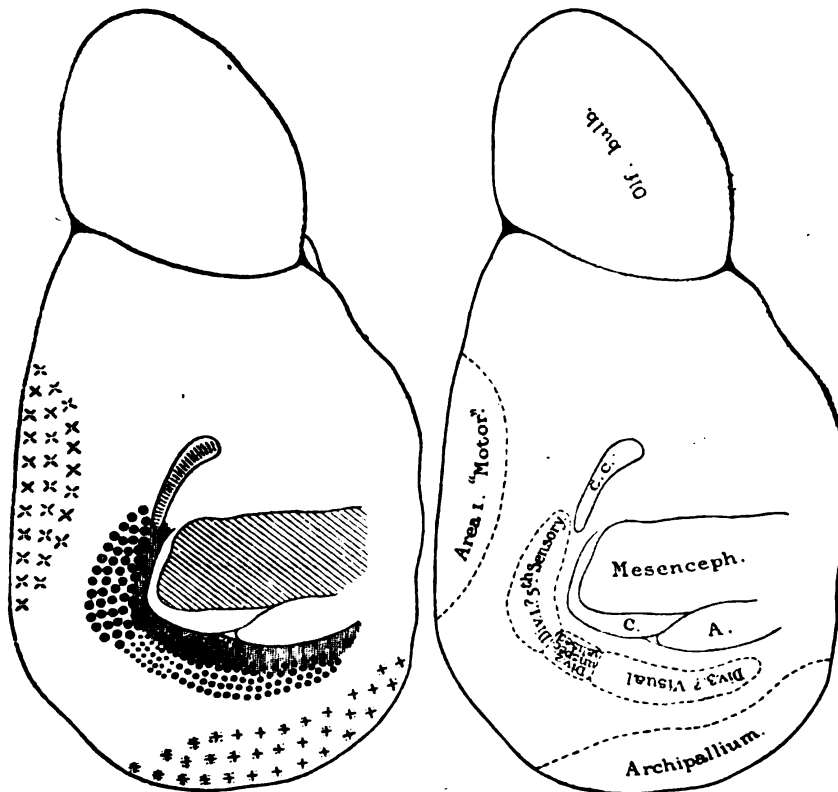


FIG. 4.—POSTERO-MESIAL ASPECT OF THE LEFT HEMISPHERE OF THE HEDGEHOG, FOR COMPARISON WITH FIG. 8 (MOLE).

NOTE.—Division 2 as explained in the text (see footnote, p. 77) is better termed "undifferentiated" than "unspecialised."

(1) *Anterior Surface*.—This presents a small olfactory field similar in structure and relative extent to that described in the Mole.

(2) *Mesial Surface*.—This may be divided into (a) the anterior straight portion, and (b) the curved postero-mesial portion (see fig. 4).

(a) *The anterior straight portion.*—(1) In about the anterior quarter of this is an area with unspecialised and undifferentiated features continuous with the similar cortex on the anterior part of the dorsal lateral surface (antero-mesial area of undifferentiated cortex). (2) Behind this the cortex is somewhat better developed, although not markedly specialised as regards its lamination. (3) Superiorly and posteriorly to the latter region the sensori-motor area (with modified characteristics) extends over, from the dorsal

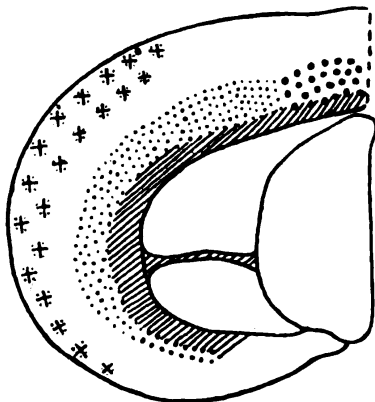


FIG. 5.—POSTERIOR ASPECT OF THE LEFT HEMISPHERE OF THE MOLE: SIGNS AS IN FIG. 3. FOR COMPARISON WITH FIG. 6. (HEDGEHOG).

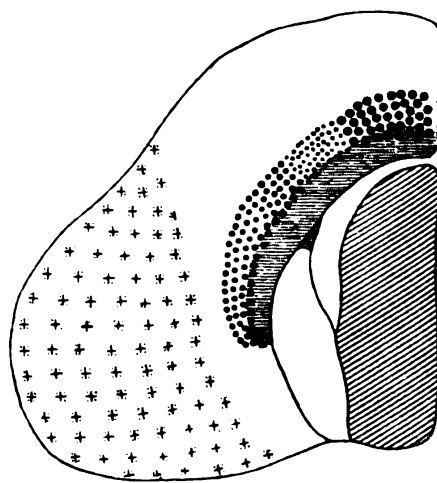


FIG. 6.—POSTERIOR ASPECT OF THE LEFT HEMISPHERE OF THE HEDGEHOG. FOR COMPARISON WITH FIG. 5. (MOLE).*

* NOTE.—The right hand figure (Hedgehog) relatively to the left is reduced.

aspect relatively to about the same extent as in the Mole, whilst inferiorly and posteriorly is the commencement of the highly specialised field to be now described.

(b) *The curved postero-mesial portion.*—Owing to the hemisphere being less flattened the postero-mesial region is not so curved in the Hedgehog as in the Mole. This will be evident from the diagrams (figs. 3 and 4, pp. 73 and 83), and in figs. 5 and 6 of the posterior aspect it is seen that the basal pallium extends considerably further round on to this surface in the Hedgehog than it does in the Mole. As in the case of the latter animal this region has been studied, not only in sagittal and coronal sections, but also in serial

sections made from blocks cut as transversely to the region as possible in various parts of its course. Just as was seen in the Mole, this region in the Hedgehog presents a tongue of neopallium (less curved for the reason stated) having highly specialised features (see figs. 4 and 6). This tongue, which extends a short distance forwards on to the anterior straight portion of the mesial surface, is inserted between, on the one hand, the mesial portion of the overlapping sensori-motor area, and the cortex behind and below this, including archipallium, and on the other the posterior part of the corpus callosum and the hippocampus, although separated from the latter by a thin band of different but characteristic cortex composed chiefly of long pyramid shaped cells. The relations of this specialised area to the remainder of the cortex coating the postero-mesial region will be sufficiently gathered from this description, from the diagrams and from comparison with the Mole. It should be mentioned that this area also occupies part of the ventral surface of the hemisphere overhanging the hippocampus, and in its lower part is almost confined to this—a point which could not be clearly figured in the diagrams.

Taking the specialised area as a whole its lamination may be said to be constituted by (see Plate IV., photo 11), a deep molecular layer, a shallow, but for the most part fairly definite, supra-granular layer, a "granular layer" containing only small pyramid shaped or angular cells and a deep infra-granular portion of cortex. Instead, however, as in the homologous area in the Mole, of the "granular layer" being made up of a closely packed formation of small cells, the elements of this layer in the Hedgehog are larger, more spread out and irregular in distribution, causing the limits of this layer to be more difficult to determine. The presence of a shallow supra-granular layer should also be noted (compare microphotos, Plate II., photo 5, with Plate IV., photo 11).

Owing to certain differences in different parts this specialised area has been separated, as in the Mole, into three divisions—a superior and inferior characterised by

well developed and differentiated cortex, separated by a middle division which shows comparatively undeveloped features (see figs. 4 and 6).

(1) *The superior and anterior division* (Plate IV., photo 11).—This is of about the same relative size as in the Mole. The supra-granular layer is composed of cells some six or eight deep, closely packed together. The cells, although smaller, have much the same form as have the elements of the supra-granular layer in the sensori-motor area and have good processes; further they are on the same cortical level as those of the supra-granular layer in the superior adjoining neopallial region. Below the supra-granular layer is a clearer space containing numerous more scattered cells, small pyramidal or angular in shape and generally erect—this constitutes the “granular” layer. Subjacent is a deep infra-granular portion of cortex containing well formed cells, many in the upper part being darkly staining and long pyramidal in shape, whilst some are fairly large pale cells of the Betz type with small Nissl bodies. A faint but fairly constant depression in the molecular layer, having the appearance only of a vascular groove, runs along the middle of this region (see photo 11).

(2) *The middle division* (Plate IV., photo 12).—On reference to the diagrams (figs. 4 and 6) it will be observed that this field is relatively much smaller in the Hedgehog than in the Mole. In its widest part it is narrower than is the superior division in a similar situation. Its histological characters differ from those of the superior division, particularly in that its lamination is very irregular and in that all the cell elements comprising the different layers, including the “granular,” are more embryonic in appearance. The supra-granular layer is even more feebly developed and there is a distinct diminution in the numbers and in the size of the larger elements of the infra-granular cortex.

(3) *The inferior division* (Plate IV., photo 13). This is relatively considerably more extensive, both as regards length and breadth, and is a more histologically distinct field than in the Mole. Well developed cells are found in all the cortical laminæ, and in this respect this division more

resembles the superior in contradistinction to the middle division of the area. The supra-granular layer is composed of small well-formed cells, five or six deep, similar to those in the corresponding layer in the superior division but more distributed. There is a deep "granular" layer, deeper than in the superior division, containing small cells, pyramidal or angular in shape, but more scattered and spread out than are the cells of the same layer in the superior division. In the upper part of the fairly well developed infra-granular cortex are considerable numbers of the pale cells of the Betz type, which cells also occur occasionally in the granular layer.

The line of demarcation between the different divisions of the field is not a sharp one. In the superior division the cortex posteriorly begins to lose its chief features, so that it gradually shades into that of the less differentiated region (middle division (2)). Similarly the inferior division (3) in its upper part shades into the middle division, whilst in its lower part the lamination becomes less definite, until the features characteristic of the field ultimately fade away. The description given of the cortex of the three divisions of the area has been taken from the portions where the features in their structure showed most prominently and characteristically.

The postero-mesial specialised area in the Hedgehog still retains the features which have been referred to in the instance of the corresponding area of the Mole as characteristic of the hippocampal type of cortex. But the structure of the cortex in this area in the Hedgehog shows a slight advance upon that seen in the Mole, in that it presents a fairly definite, though rudimentary, supra-granular layer.

Comparison of the Cortical Areas in the Mole, Shrew and Hedgehog, with Conclusions as to their Functional Significance.

Owing to the general similarity between the cortex of the Mole and the Shrew, the following observations concerning the Mole may be taken as applying also to the Shrew, excepting when the latter is specially mentioned.

(1) *The postero-mesial area of specialised cortex.*—As a matter of convenience this area will be considered first. A general account of this field has been given (Mole, p. 73, Shrew, p. 78, Hedgehog, p. 84), but the following predominant features it presents may be recapitulated.

The area is characterised by a well marked granular layer, which, especially in the Mole, owing to its definiteness, and owing to the practical absence of the supra-granular layer, constitutes the most prominent feature of the cortex. By means of certain differences of detail presented the area has been separated into three divisions in each animal.

The superior division (1) is of about the same relative size in the Mole as in the Hedgehog: in both it is characterised by granular and infra-granular cortex made up of well developed cell elements, and in the Hedgehog by a shallow but definite supra-granular layer.

The middle division (2) is relatively and actually considerably larger in the Mole than in the Hedgehog, but in both, although the cortex presents specialised features, the cells composing it are comparatively undeveloped and undifferentiated.

The inferior division (3) is relatively not only considerably larger in the Hedgehog than in the Mole, but in the former is a more histologically distinct field, the cortical layers of which are made up of well developed cells. In the Shrew this division is perhaps rather better developed than in the Mole.

Owing to the presence throughout this area, as a whole, of such a deep and definite "granular" layer, it is concluded that this relatively extensive region is sensory in function.

The middle division (2) may be dismissed from consideration at the present time, as it presents comparatively undifferentiated features. In the Mole, although the granular layer is deep, the individual cell elements it contains are poorly developed, and the infra-granular cortex is rudimentary. In the Hedgehog the same comparatively embryonic appearance of the cells is seen; the infra-granular cortex is poor in character, and the supra-granular layer found in the superior and inferior divisions of the area

almost disappears. Thus it would seem that this middle division has not the connections nor the physiological importance of the superior and inferior divisions, although histologically it separates the two latter, and probably indicates that they are different functional areas.

There remain, then, for consideration *the superior and inferior divisions* 1 and 3.

Hermanides and Köppen have recognised in the cortex of the Mole the region in the posterior portion of the hemisphere characterised by the prominent "granular" layer, and although the orientation details given in their paper are not very complete, the region mentioned by them possessing this feature no doubt corresponds to that which the writer has described as the postero-mesial specialised area. The authors alluded to conclude, from the presence of the granules and by analogy, that the area in question is visual in function. The possession of a prominent granular layer is by itself, however, probably only sufficient evidence that a given area is primarily sensory in function. As vision in these Insectivorous mammals is so limited, and the optic nerves, especially in the Mole and Shrew, are so diminutive, it is probable that their cortical visual field is also rudimentary. By means of the methods adopted the writer has convinced himself that the postero-mesial region of cortex, characterised by a very prominent granular layer, is relatively a large one, but he believes that it is divisible into two differentiated areas separated by one which is comparatively undifferentiated.

Regarding the postero-mesial specialised area and its divisions the following suggestions are made :—

(1) The area as a whole is much too large to be concerned only with the ultimate cortical distribution of the optic nerves.

(2) *The inferior division* alone represents the cortical visual area. Some support is lent to this view by the following facts: In the Mole, an animal of underground habits, in which vision is of little practical use, and in which the optic nerves are minute, this portion of the specialised area is small, indefinite, and its lamination is irregular.

In the Shrew (of somewhat similar habits) it is, perhaps, slightly better developed. The Hedgehog, although preferably a nocturnal animal, appears to have distinctly better vision than the Mole and Shrew, and relatively larger optic nerves. In the first-named animal the portion of the area in question is considerably more extensive, comparatively, than in the two latter, it seemingly having developed in an upward direction and partially absorbed the field of undifferentiated "granular" cortex (the middle division (2)), which in the Hedgehog is relatively small. The lamination also of this division of the area in the latter animal is distinct; there is a deep and well developed infra-granular cortex and a shallow supra-granular layer. It is, perhaps, worthy of special mention that in this division of the area the Hedgehog alone of three animals presents in the infra-granular cortex numerous large cells (many of which are pale, with small chromophilic elements), the probable analogues of the solitary cells of Meynert.

(3) *The superior and middle divisions* of this area are homologous to the large supra-callosal (*i.e.*, infra-calcarine-intercalary) area of certain relatively higher mammals, a considerable portion of which area in such mammals exhibits definite sensory characteristics.*

On account of the probable importance of the fifth sensory nerve as an avenue of information through snout touch or vibrissæ sensation, or both, to many lower mammals (*e.g.*, Insectivora), and in view of the relatively very large size in these of the fifth nerve, it seems not unlikely

* Campbell has mapped out the area in question in the Cat, Dog and Pig, and refers to it under the Limbic type of cortex. According to the writer's observations, as yet unpublished, on the brains of mammals belonging to several different natural orders, the cortex included under Campbell's Limbic type, variation B (which the present writer thinks may be the homologue of the superior division of the postero-mesial specialised area in the Insectivora) is characterised by a well marked granular layer. The region referred to is, perhaps, better termed "supra-callosal" (although this description is not strictly anatomically correct) than "infra-calcarine," so as to avoid confusion with the infra-calcarine area of the Primates. Owing to the extension backwards of the posterior part of the hemisphere in the latter, the calcarine fissure has become oblique, so that the "supra-callosal" region is really "supra-calcarine."

that the sensory portion of this nerve has a very special cortical representation. Further, and chiefly by a process of exclusion, there seems to be some basis for the assumption that the comparatively well developed cortex having sensory characteristics found in the superior division of the postero-mesial specialised area in the Insectivora, is concerned with the cortical sensory distribution of this nerve.*

It should be stated that by the "fifth nerve sense" here referred to is understood merely a form of superficial tactile sensibility, perhaps highly elaborated in certain lower mammals. It is presumed that superficial tactile impressions in connection with the snout, or vibrissæ, or both, have become in these animals of such importance that they have come to have a very special cortical representation. Kinæsthetic impressions arising from movement of facial muscles (snout), and perhaps from muscular and sub-epithelial tactile sensations connected with vibrissæ, are presumably represented elsewhere, *i.e.*, in the area of kinæsthetic representation generally. If this view is tenable the so-called fifth sensory nerve area as provisionally located in the Insectivora would be merely part of a much larger cortical area concerned with general superficial tactile sensibility, which area would also have developed had general tactile sensations been of the same (or of any considerable) importance towards the survival of these animals as is probably the "fifth nerve sense."† Histo-

* A point in favour of the view that this portion of the "supra-callosal" or "infra-calcarine" region is not concerned with the sense of smell, is the fact that in the Porpoise (a Cetacean the brain of which presents general fissural homologies showing its alliance with the Ungulata [Elliot Smith]), the above-mentioned region remains, macroscopically at least, intact, although there is entire absence of the olfactory bulb and tract, and atrophy of the greater part of the remainder of the olfactory apparatus.

See also Notes to figs. 7, 8, 9.

† The use which the Hedgehog makes of its snout has frequently been noticed. A freshly caught Mole was placed by the writer in a large glass case, which had previously been filled with earth. When it came to the sides of the case, as it often did in its burrowing operations, its mode of procedure could be readily watched, especially as for some distance its tunnel was continued along one or other side of the case, which thus formed, so to speak, one wall of the burrow. The animal seemed considerably puzzled at first by the glass, and appeared to investigate it with its snout, touching it

logical evidence in the Insectivora is insufficient to warrant the assumption that the region on the mesial surface of the hemisphere anterior to the so-called "fifth nerve area" and below the "modified motor" is characteristically sensory at all, much less, of course, that it is concerned with tactile sensibility.

If this interpretation of the significance of the postero-mesial specialised area is correct, it follows that in the Mole and Shrew the visual cortical field is a mere vestige, and confined to the lower limits of this area. In the Hedgehog the same field is more extensive in both upward and lateral directions, and is better developed. In higher forms (*e.g.*, Ungulata and Carnivora), in which the visual faculty is of greater importance, this field has further extended upwards, backwards, outwards and forwards, has developed gross cortical connections as the "visuo-sensory" area, and has come to overlies the region which, in these animals, would correspond to the superior and middle divisions of the postero-mesial specialised area in the Insectivora. In the lower part of the newer cortical field the calcarine-intercalary (lower mammalian) fissure has appeared sharply separating the visual area from the region below. As a corollary to this interpretation it may be added that in still higher forms (Primates), with the development of the parietal association centre, the visuo-sensory area becomes pushed backwards and towards the mesial surface.

These views are put forward at the present time in only a tentative manner. Much further work is necessary in order to establish their accuracy.

In the Cat, Dog and Pig, Campbell describes the visual area as occupying an extensive field on the mesial and dorsal aspects of the hemisphere, roughly that limited by the calcarine-intercalary fissure on the mesial aspect, then passing round the occipital pole, and extending on to the dorsal surface as far as the hinder limits of the sulcus

lightly and rapidly in all directions. Although the snout did not seem to be used in actual burrowing, this, with the head, appeared to be employed after the manner of a drill in the soil, which had been previously loosened by the forelimbs.

lateralis—minor variations of distribution existing in the several animals. The area is in all characterised by a fibre line considered by this author to be the homologue of the line of Gennari. From his own observations the writer believes the above account of the distribution of the visual area in these animals to be approximately correct, and he has found an area of similar distribution and having similar characteristics in other Ungulates and Carnivores, also in certain Rodents. The writer was, therefore, at first inclined in the case of the Insectivores examined to look for the visual area in what may be considered to be the corresponding region in these animals, viz., the region which has been designated the postero-mesial area of undifferentiated cortex. Failing, however, to find in this area any lamination which he believed to be characteristic of sensory cortex he was compelled to look elsewhere for the cortical distribution of the optic nerves, hence the above explanation of the significance of the divisions of the postero-mesial specialised area which has been tentatively submitted.

It might be argued that such visual cortical representation as these Insectivores possess may actually lie in the field designated the postero-mesial area of undifferentiated cortex, and that such field might have undergone atrophy and have lost its most characteristic features. That the cortex of the area in question does show a lack of depth as compared with that of the better developed areas 1 and 2 may appear to lend support to this view, but against it is the fact that the area has remained very extensive, especially for an animal like the Mole which is possessed of such minute optic nerves. It is, however, of more importance to note that the area does not present, in its cell lamination, features characteristic of a projection sphere at all, and one would not have expected in an atrophied cortex to have found the later developed supra-granular layer persisting so relatively well as it has done in the area in question. The writer believes that the features presented by this region of the cortex are rather those of under-development and non-differentiation of an associational area than of atrophy of a specialised projection sphere.

Diagrams of the postero-mesial region of the left hemisphere in (i.) an Insectivore; (ii.) a Carnivore or Ungulate; (iii.) in Man, to illustrate the suggested relations and variations of the area of specialised cortex characterised by a prominent granular layer.

The portion of cortex termed division 3 in fig. 9 is an approximate representation of the "visuo-sensory" area in the human subject as mapped out histologically by Bolton.

FIG. 7.—In the Insectivore the specialised cortex above referred to is confined to the postero-mesial surface, and is believed to be histologically separable into three divisions: (1) ? fifth sensory; (2) undifferentiated; (3) ? visual.

FIG. 8.—In the Ungulate and Carnivore, division 1 has much the same position, allowing for differences in shape of the hemisphere, but is variable in extent in different animals. Division 3 (visual) has greatly extended (as compared with the Insectivore) backwards, upwards, outwards and forwards; has reached the dorsal aspect, and has come to overlie division 1. In this new field the calcarine-intercalary fissure develops, sharply separating divisions 1 and 3.

FIG. 9.—In the Primate, owing to the extension backwards of the hemisphere (Elliot Smith), and owing to the development of the parietal association centre, especially Fleschig's precuneal centre, the calcarine fissure and with it the "visuo-sensory" area (division 3) has become oblique.

Whether the so-called division 2 in the Carnivore, &c., and Primate, persists or becomes absorbed in division 3 is at present uncertain. Division 1 in the Primate also loses some of its characteristic features.

(i.) INSECTIVORE.

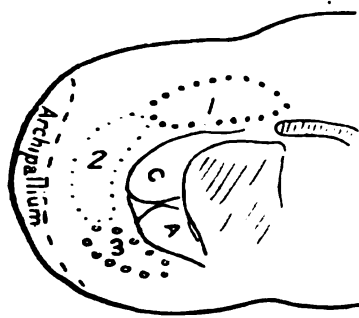


FIG. 7.

(ii.) CARNIVORE OR UNGULATE.

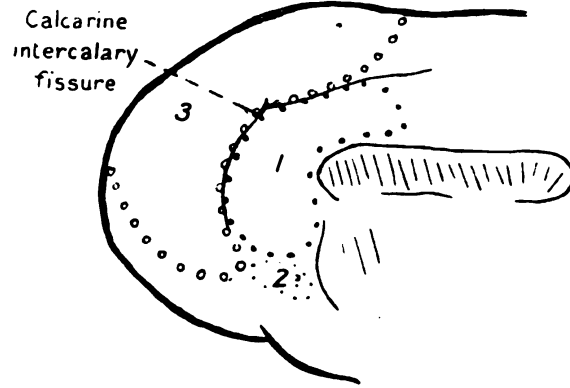


FIG. 8.

(iii.) MAN.

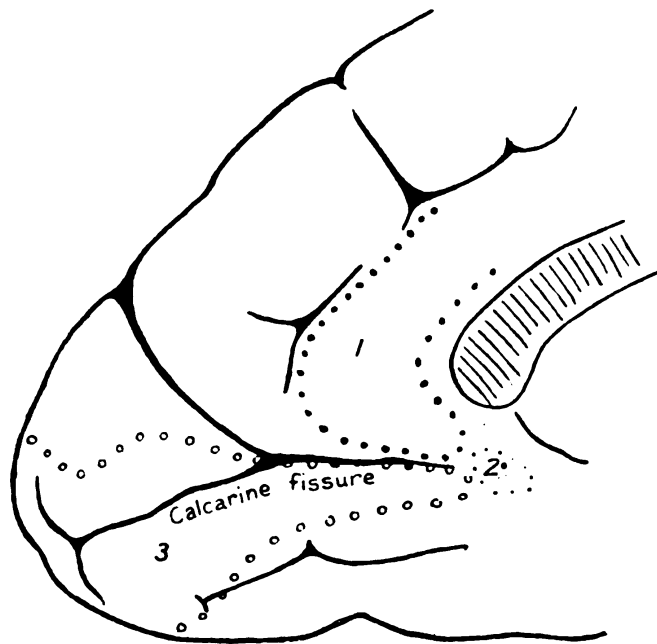


FIG. 9.

(2) *Areas 1 and 2. Motor and general sensory.*—It has been stated that in the Mole the large dorso-lateral field of comparatively well developed neopallium can be readily sub-divided into two areas, owing to certain characteristic histological features. In the internal portion of the field the upper part of the infra-granular cortex presents numerous large pyramid shaped cells, the analogues of the Betz cells, and contrasted with the appearances in a similar situation in the cortex of the Hedgehog these cells have an orderly and regular arrangement. In the lateral portion of the field these cells are less numerous and rather smaller, although more spread out, whilst here there is an appreciable increase in the depth of, and of the number of cells in, the granular layer. Hence, on histological grounds, it is concluded that the internal portion of the field (area 1), possesses motor attributes, and the external portion (area 2), sensory. In the Shrew the two areas may be similarly separated, although the main difference between them lies in the increased depth and prominence of the granular layer in the lateral area (2), as compared with the internal area (1). In the Mole and Shrew these two areas are relatively of about the same size. In the case of the Hedgehog the writer was unable, after many attempts, to arrive at any altogether satisfactory criteria which would enable him, from cell lamination alone, to subdivide this extensive dorso-lateral field, hence he considers that although there may be some attempt at specialisation, it is probably more correct to regard the whole of this field in the Hedgehog as a combined sensori-motor area.

The explanation of these structural differences between the Mole and Shrew, on the one hand, and the Hedgehog on the other, which suggests itself, is that they stand in relation to the fact that the former animals are possessed of more numerous and better motor accomplishments than the latter animal, and so have a more specialised zone of motor cortex, and a more regular and orderly arrangement of the constituent cells. It is well known that the Mole, apart from its underground operations, is a very active animal, as also is the Shrew, whilst the Hedgehog is com-

paratively lethargic and slow moving, its survival having been dependent rather upon its adoption of a protective armour of spines than upon its energy and activity.

Gustav Mann as the result of his stimulation experiments on the brain of the Hedgehog found centres for head movements in front of the "transverse" (presylvian) sulcus, whilst behind it he located internally centres for the limbs, and externally an extensive centre for eating movements, the latter apparently reaching as far as the rhinal fissure. Although the region of excitable cortex thus described is more extensive it agrees, as regards its main focus, with the "sensori-motor" area as mapped out by the writer histologically in the Hedgehog.

Area 2. General sensory.—With regard to the area which has been termed "general sensory" it seems not improbable that this is largely concerned with "kinæsthetic" impressions. Miss Jessie Allen's very complete and carefully controlled experiments upon the "associative processes of the guinea-pig," show that in this animal the factors of greatest importance in recalling a path, are the sensations of running, turning and other movements,—hearing, vision, smell and touch are of less importance. She concludes: "The most important senses with the guinea-pig are the kinæsthetic. We can almost say that the guinea-pig does the greater part of its remembering in kinæsthetic terms." The writer has personally made some observations, extending over several years, and chiefly also upon guinea-pigs, which fully confirm many of Miss Allen's conclusions.

It seems certain that this kinæsthetic faculty is of very great importance to many lower mammals. To one like the Hedgehog, which prefers to move about in the dusk or the dark, it should be useful, and especially so to one like the Mole, in which, probably, it constitutes the basis of the animal's memory of its way about its elaborate system of subterranean galleries. In these Insectivora it would appear that the field designated areas 1 and 2 in the Mole and Shrew, and the combined areas in the Hedgehog, is one of the oldest parts, phylogenetically, of the neopallium, and in every sense the best developed. It would seem that the

kinæsthetic sense is the first to have important and fairly complete neopallial representation, and to constitute a large part of the basis of such *intelligence* as these animals possess. Reference has already been made to kinæsthetic impressions, probably arising from deep snout touch, and from muscular and deep (sub-epithelial), sensations in connection with the movement of vibrissæ. The importance of these as a source of information to the animal need scarcely be insisted upon.

The Eighth nerve Area.—Reasons have been given for the belief that in the Insectivora eighth nerve impressions have only a comparatively feeble cortical representation. This has been located provisionally, and not on very definite grounds, in approximately the anterior part of the region, which, as a whole, has been designated the lateral area of undifferentiated cortex.

Areas of undifferentiated cortex.—The three areas so designated have been described as being characterised by the possession of no definitely specialised features in their lamination and by the poorly developed (*i.e.*, comparatively embryonic) condition of the individual cell elements found in the several layers. Some slight modifications exist in the three areas, the under developed condition being a little most obvious in the antero-mesial area, and certain indefinite sensory features being exhibited by, roughly speaking, the anterior part of the lateral area. Whilst the writer does not feel justified in attempting to attach any peculiar functional value to these areas and concludes that it is advisable to regard them as indifferent and unspecialised portions of cortex, such features as are shown by their lamination on the whole suggest that they may perhaps be regarded as attempts at the production of cortex of an associational type, although they do not individually stand in direct relation to any of the projection spheres.

FUNCTIONAL SIGNIFICANCE OF THE CEREBRAL CORTICAL LAYERS (neopallium).

General Remarks.—Although a considerable amount of work has been done by the writer upon the structure of the cerebral cortex in mammals belonging to other natural

orders, which supports the conclusions presently to be detailed as to the functional value of the cortical layers, in this paper reference will be made only to the Insectivora examined, and especially to the supra-granular (pyramidal) and infra-granular cortical layers. The sense in which these latter terms are used has already been stated (p. 61).

The total depth of the cerebral cortex differs considerably in the Mole, Shrew, and Hedgehog. A rough idea of these differences will be obtained on comparison of the photomicrographs of strips of the cortex from corresponding regions in the respective animals (see Plates I. and III., 1, 8, 10). That there should be marked differences in the total depth of the cortex in the various animals is, from several considerations, only to be expected. As Bolton has shown, in mammals possessing a convoluted brain it is only by taking average measurements of what he terms the "flat" surfaces, "apices" of a convolution, and the "sides" and "bottoms" of a fissure that the correct total depth of a given cortex can be estimated. In the so-called lissencephala, without, or rather with few and only insignificant true neopallial fissures, one has not the help which definite fissures afford in determining the exact total average depth of the cortex, which depth in such brains is dependent doubtless upon several factors. One of such factors which certainly appears to be of much importance is the manner in which the hemisphere is shaped. This is illustrated by figs. 10 and 11. In the Mole, for example, owing to the contour of the hemispheres, the greater part of the dorsal surface of the cerebrum is covered by simple straight cortex, best comparable perhaps to that of the flat surface of a convolution. Thus the depth of this cortex probably approximates to the general average depth, which would be obtained on measurement did the neopallium present definite fissures of any considerable depth. In the cortex of the Hedgehog, on the other hand, there is very little if any real flat surface at all, because the entire hemisphere in this animal is so moulded that its mantle is more like that of the much rounded apex of a gyrus, fibres streaming to and from it in many radiating directions. This factor

alone would account for some absolute increase in depth of cortex—particularly of the infra-granular portion—in the Hedgehog as compared with the Mole. Other factors which doubtless exercise considerable influence upon the total depth of the cortex are the actual size of the constit-

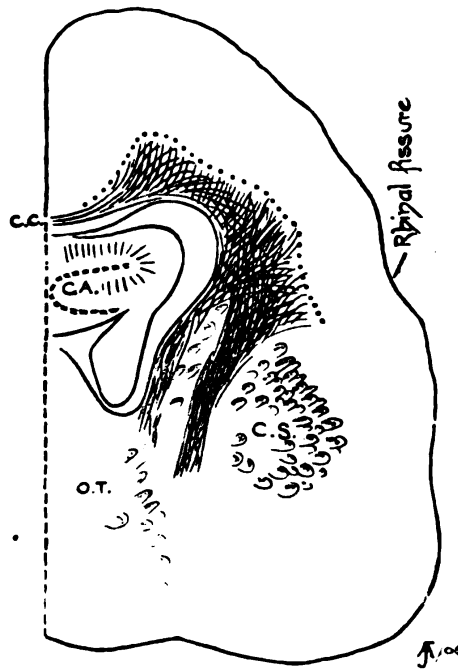


FIG. 10.—THE HEDGEHOG.

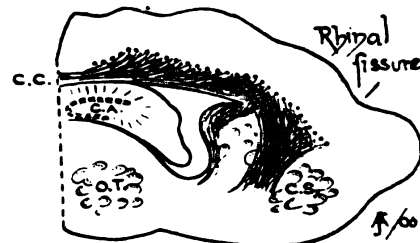


FIG. 11.—THE MOLE.

FIGS. 10 and 11.—Outline drawings, to the same scale, of coronal sections of one cerebral hemisphere, at about its middle, of the Hedgehog and the Mole, to show the difference in shape of the hemisphere, and the influence of this difference upon the total average depth of the cortex (see text). The dotted line = the lower limit of the grey matter; the straight and oblique lines (shaded part) the central white core, which is narrower and deeper in the Hedgehog than in the Mole. The cortex of the Hedgehog thus corresponds, *on the whole*, to a rounded apex of a convolution; that of the Mole to a flat surface.

uent nerve-cells, and the distances from one another at which these are situated (see photos 1, 8, 10). In the Shrew the cells are, on the average, small, and comparatively closely crowded together; in the Hedgehog they are actually considerably larger, and the intervals between them relatively much greater. In both the above-mentioned respects

the Mole occupies a position intermediate between the Shrew and Hedgehog, as it does in total depth of cortex. It is a point perhaps worthy of special mention that the average size of the constituent nerve-cells of the cortex in these three animals belonging to the same natural order is related to the size of the animal. Incidentally attention may be drawn to the fact that the Hedgehog would thus appear to possess a relatively and absolutely much greater amount of so-called intercellular substance than does the Shrew, or even the Mole—a fact which should be of interest to those who lay stress upon the functional importance of this substance.*

For the reasons given it appears to the writer that great care should be exercised before any definite conclusions are drawn concerning the significance of the total depth of the cerebral cortex, and it is felt that as regards total depth of cortex *per se* the three animals included in this series cannot and should not be compared. Fortunately, for the writer's present purpose this is a secondary matter, because the relative depths of the separate cortical layers, particularly the supra- and infra-granular, is approximately the same in all; indeed, if the above-mentioned factors which assist in determining total depth of cortex are taken into consideration, it is probably very approximately the same.†

* See Nissl's comparison of the cortex of the Mole, Dog and Man, and the conclusions drawn therefrom (*Munch. med. Wochensh.*, Bd. xlv., 1898, S. 1027, figs. 3, 4 and 5; figures reproduced in Barker's "Nervous System," pp. 97-99). It can hardly be maintained in this connection that the Hedgehog displays evidence of the possession of a much greater degree of psychic, or indeed of any other activity, than that shown by the Shrew or Mole. Compare photos 8 and 10.

† The Mole in respect of depth of supra-granular has perhaps a slight relative advantage over the Hedgehog. The diminution in depth of the supra-granular in relation to the infra-granular cortex in the latter animal, as compared with the Mole, is probably more apparent than real, and is due to the shape of the hemisphere. The depths of layers 4 and 5 (infra-granular) are always greater at the apices of a convolution, and as has been stated, the hemisphere in the Hedgehog is moulded after the fashion of an apex, although not an extreme or pointed apex. Had the hemisphere presented a more or less flat surface, as in the Mole, it is reasonable to suppose that the relative depths of supra- and infra-granular layers in the Hedgehog would have approximated even more closely to those of the Mole than they do.

Micrometric measurements of the cortex of the Mole.—Dr. Bolton has kindly furnished the following micrometric measurements of the cortical layers in three different areas of the neopallium of the Mole. These measurements nearly coincide with some rougher estimations previously made by the writer, but of course the former are much the more valuable, owing to their almost mathematical accuracy. Further, as it was intended to make a comparison of the depths of the cortical layers in these animals with those found by Bolton in the human subject, it was desirable that all the measurements made use of should be undertaken by the same observer, so that any personal equation involved in the matter should remain as far as possible constant. With the exception perhaps of a portion of the posterior undifferentiated region of cortex, the areas from which the measurements have been taken are the only ones which could supply measurements of all the cortical layers at all comparable with one another. For example, it will be readily understood that in the postero-mesial region of specialised (sensory) cortex, from mechanical considerations alone, *all* the cortical layers could not be measured for any very accurate comparative purposes, the region being curved in more than one direction, and no assistance being derived from the presence in it of any definite fissures.

MICROMETRIC MEASUREMENTS OF THE CORTEX OF THE MOLE.

		Area 1. Motor (average of 23)		Area 2. General sensory (average of 17)		Lateral area* (average of 7).	
Layer		mm.	mm.	mm.	mm.	mm.	mm.
	i.—Molecular ..	0.162		0.144		0.095	
	ii.—Supra-granular ..	0.092	0.320	0.093	0.367	0.095	0.320
	iii.—Granular ..	0.228		0.274		0.225	
	iv.—Infra-granular ..	0.147	0.304	0.176	0.377	Not se- parated	0.471
	v.— ..	0.157		0.201			
Total		0.786 mm.		0.888 mm.		0.886 mm.	

* With regard to the lateral area of undifferentiated cortex, the cellular elements in which are comparatively unspecialised, it is obvious that its increase in depth as compared with area 1 is due chiefly to the infra-granular layers (iv. and v.), the portion of the cortex from which the measurements were taken being in the neighbourhood of the rhinal fissure, and so forming what would correspond to the apex of a convolution.

It will be observed that in area 1 the supra-granular layer (ii.) is less than one-third the depth of the combined infra-granular layers (iv. and v.), and that in area 2 it is only about one-quarter of the depth of the latter. If layers ii. and iii. (supra-granular and granular) are taken together they only approximately equal in depth the combined layers iv. and v. (infra-granular).

In the case of the Shrew, in which, owing to the orderliness of the cortical lamination, measurements of the layers are as easily made as in the Mole, the same relative depths of the cortical layers practically hold good. In the Hedgehog, because of the extreme irregularity and variability in depth of the supra-granular layer, and because of the indefiniteness of the granular layer, accurate measurements of all the layers are extremely difficult, and no doubt a considerable personal equation would be involved in such measurements. At the same time a probably approximately accurate separation into supra- and infra-granular portions of cortex can be made, and when this is done it is found that (with the reservation due to shape of hemisphere to which attention has been directed) about the same relative depth of these portions of cortex is preserved in the Hedgehog as was seen in the Mole and Shrew.

A comparison is of interest between these measurements in the Mole and those of Bolton from the prefrontal cortex, in the cases of normal human aments (foetus and new-born child) and the normal human adult. The measurements are graphically shown in the following table.

It would, perhaps, have been preferable to have contrasted the measurements of the cortical layers in the area designated "motor" in the Mole with those of the same layers in the human "excito-motor" region, but in the first place the writer is unaware of any published systematic measurements of the layers in this region of the human cortex. Moreover, it is more than doubtful if the areas referred to in the Mole and the human subject respectively can be regarded as strictly homologous. Measurements are available from the "visuo-sensory" (projection sphere) and from the visuo-psychic and prefrontal (centres of associa-

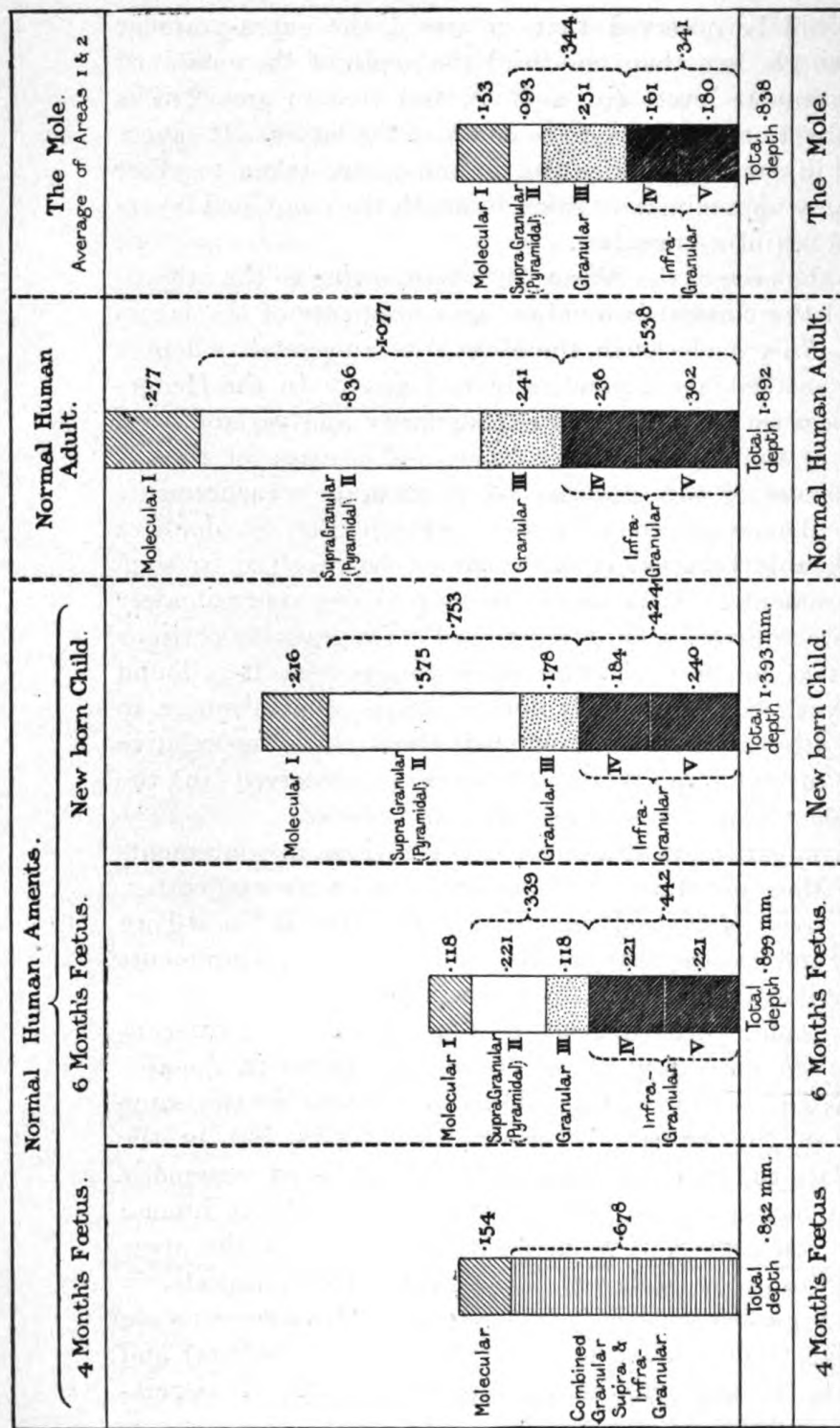


FIG. 12.

Illustrates approximately the relative depths of the cerebral cortical layers in normal human aments (four and six months' fetus and new-born child), the normal human adult and the Mole.

The micrometric measurements in the first four cases are taken from "The Histological Basis of Amentia and Dementia" (*Archives of Neurology*, vol. ii., 1903) by J. Shaw Bolton; those of the cortex of the Mole are also by Dr. Bolton, Supra-granular (pyramidal) layer left blank; infra-granular (iv. and v.) shaded darkly.

Note to FIG. 12.—The infra-granular cortex in the six months' fetus and new-born child were practically of the same depth in the specimens measured, viz., .442 to .424. In the figure the darkly-shaded part (infra-granular cortex) in the third column is shaded.

tion) regions in the human subject. It would be justifiable to make use of measurements from any one of these regions in this connection, as it is merely desired to emphasise in a general way, but from the developmental aspect, the functional significance of the cortical lamination. As the measurements in the case of the Mole are calculated from the average of those of the two best developed regions of cortex which this animal possesses, and as by some it may be considered that the prefrontal area does not represent one of the highest structurally evolved regions of the human cerebrum, the advantages—if there are any—in the subjoined comparison are on the side of the Mole.

Reference to the above table shows that the total depth of the cortex in the four months' foetus examined was almost exactly that of the adult Mole.

It will also be seen on comparison of Bolton's figures concerning the human cortex that the infra-granular portion of the cortex had, even in the six months' foetus, already attained by far the greater proportion of its ultimate adult average depth. The very fact that whilst the depth of the supra-granular layer in the full-time child had much exceeded the depth of the same layer in the six months' foetus (.575 to .339), the infra-granular portion in the instances examined was slightly less deep in the full-time child than in the six months' foetus (.424 to .442), is a point in favour of the lower functional significance of the latter level of the cortex. As regards the supra-granular layer, it will be found that in the six months' foetus this layer was half the depth of the infra-granular (iv. and v.), or the same as the polymorphic alone. In the full-time new-born child the supra-granular had exceeded in depth the infra-granular (1.3 to 1). In the normal human adult the supra-granular layer was over one and a half times the depth of the infra-granular, and if the polymorphic layer be taken alone it was 2.7 times the depth of this layer.

A general comparative summary and analysis of the figures in the above table concerning both the Mole and the human subject reveals the following facts:—

- (1) The *granular layer* is of approximately the same

depth in the Mole (average of areas 1 and 2) as in the normal human adult prefrontal cortex.*

(2) The *supra-granular* (pyramidal) layer

(i) In the six months' human foetus is nearly two and a half times the depth of that in the Mole.

(ii.) In the full-time new-born child it is six times the depth of that in the Mole.

(iii.) In the normal human adult it is nine times the depth. If layers ii. and iii. (*supra-granular* and *granular*) are taken together (any personal equation as to level of separation being thereby eliminated, as the combined depth of these layers is a practical certainty),* it is found that in the six months' foetus and the Mole these layers together are practically equal in depth, viz., .339 to .344. In the full-time child the proportion has increased as 2.2 to 1 in favour of the human subject. In the normal human adult the combined layers ii. and iii. are over three times the depth of these combined layers in the Mole.

(3) The *infra-granular layers* (iv. and v.). In great contrast to the depth of the *supra-granular* layer in the Mole on the one hand and the human subject on the other, the depth of the *infra-granular* portion of the cortex is found to be as follows:—

(i) In the six months' foetus and full-time child the combined layers iv. and v. are approximately of the same depth as in the Mole.

(ii.) In the normal human adult these combined layers are only a little over half as deep again as in the Mole (1.56 to 1).

Leaving out of consideration the average size of the constituent nerve cell—which factor would probably affect the *supra-* and *infra-granular* portions of the cortex more or

* The granular layer in the Mole may, from the measurements, appear to have been assigned an undue depth. It is possible that in this layer may have been included some level unspecialised in the cortex of the Mole, which would have contained definite pyramid shaped cells in its upper part, had the true pyramidal layer in this animal been better developed. The matter has, however, been judged on its merits and the somewhat clearer space below the level of the better formed pyramid shaped cells has been included in the granular layer.

less equally—it may therefore be said that the increase in depth of the human cortex cerebri as compared with that, say, of the Mole, is due *very* largely to increase in the supra-granular layer.

Amongst the inferences which may be drawn from various statements which have been made throughout this paper are the following :—

(1) The consideration of relative proportion of depth of primary cortical layers, or of groupings of these, is of more importance from the point of view of conclusions as to functional significance than is that of absolute total depth of cortex, which depth may be dependent upon several practically non-comparable factors.

(2) Regarded from the developmental aspect—ontogenetic and phylogenetic—the facts adduced support the thesis that the mammalian cerebral cortex (neopallium) is built up primarily on an infra-granular basis, *i.e.*, the infra-granular portion is the earliest to appear in the process of development, very quickly reaches maturity, and in the adult, especially if average size of component nerve-cell is taken into consideration, presents remarkably little difference in absolute depth in one of the lowest mammals and in the highest.

The granular layer may be said to be the next addition to the cortex. Ontogenetically it appears shortly after the infra-granular portion of the cortex, and it reaches its maximum development in depth and definiteness in the projection spheres of the cerebrum. The last layer of the cortex to appear ontogenetically is the supra-granular (pyramidal). It is the slowest of all the layers to reach maturity. It is scarcely existent at all in certain regions in some of, if not all, the lowest mammals, and even at its best in the latter it reaches but a slight absolute depth as compared with its depth in practically every region of the neopallium in the human subject.

(3) Whilst in the instances of individuals in a species of mammal the actual depth of a given cortical layer is probably the most important single factor, it is not the only factor to which attention must be paid when dealing with

the cortices of mammals belonging even to different species of the same family. The condition of the component nerve cells of a cortical layer as regards their degree of development, *i.e.*, their degree of departure from the embryonic type, or that seen in the young animal, is a very variable quantity in different species of mammals, as it is in different regions of the cortex in individuals of a given species. The significance of this factor is illustrated in the case of the Guinea-pig. It is well known that this animal's intelligence is of a very low order, yet in the best developed regions of the neopallium it possesses a supra-granular layer which is not negligible as regards mere depth. According to the writer's observations, however, the component cells of this layer, on the whole, advance comparatively little in the adult animal beyond their condition in the new-born animal, and it is difficult to credit the majority of them with much functional value. This similarity between the supra-granular layer of the new-born and adult animal the writer believes affords a ready explanation of Miss Allen's observation that there is in the case of the Guinea-pig no increase in complexity of psychical processes after the third day of life. It also affords a striking example of the fact that actual depth alone of a cortical layer is not to be altogether relied upon—under the circumstances above referred to—when endeavouring to compute the functional significance of such a layer.

It may be mentioned in this connection that the writer has formed the impression, judging from the condition of the nerve cells in the older and in the more recent types of mammal which he has so far examined, that very probably in the better developed regions of the cerebrum the degree of organisation of the individual nerve cell elements of the cortex bears some relation to a given animal's existence in time.

In the foregoing table (fig. 12) the factor of under-development is probably to a great extent eliminated, and even if it is not the comparison may be said to favour the Mole.



Conclusions as to the Functional Significance of the Supra-Granular and Infra-Granular Cortical Layers.

The foregoing data support the following conclusions,* which apply only to *mammals*, and which form, from the point of view of the Insectivora, and of the lower mammals belonging to various other natural orders so far examined, a complement to those arrived at by Bolton as the result of his studies of the development of the human cerebral cortical layers, and of their depth in the adult normal individual as well as in various degrees of amentia and dementia (see p. 62).

(1) The infra-granular portion of the cortex (iv. and v.) (omitting the constituent cells which possess motor or analogous functions) is concerned especially with the associations necessary for the performance of the instinctive activities, that is, all those which are innate and require for their fulfilment no experience or education. These form the basis of many complex actions necessary for the preservation of the individual and the species, such as the seeking appropriate shelter and protection, the hunting for food—each after his own kind—and the quest of the opposite sex. Although these acts may be accompanied by consciousness, there is no evidence to show that this is “focal” or that essentially they are controlled by consciousness (Lloyd Morgan). It is believed that lower mammals have provided in the infra-granular cortex (which is relatively so fully matured at birth in them as well as in man, and which in the adult, even in animals low down in the mammalian scale, reaches such a great degree of absolute development) a sufficient cerebral cortical mechanism for the performance of these lower associations. The actions which are the outcome of such associations are often complex, and as an instance of the class included under this heading the tunnelling of the Mole may be mentioned. Such more or less stereotyped actions may show signs of improvement

* In an extensive examination of the neopallium of mammals belonging to natural orders other than the Insectivora, the writer has not met with any facts which in any way invalidate these conclusions.

in their performance, firstly, as the result of perfection by use of an inherited mechanism, and secondly, as the result of the intermingling of activities for which it is concluded that the supra-granular layer is responsible. In the latter case, however, the actions would merge into those which are more properly described as habitual intelligent, or into the class of "incomplete instincts" (Lloyd Morgan), or "mixed instincts" (Romanes).

(2) The supra-granular (pyramidal) layer—which is, relatively to the infra-granular cortex, so poorly developed at birth—is slow in reaching maturity, and is, even at its best, in certain lower mammals, such as the Insectivora, only of an insignificant absolute depth—suberves the higher associations, the capacity for which is shown by the educability of the animal. It has, therefore, to do with all those activities which it is obvious that the animal has acquired (or perfected) by individual experience, and with all the possible modifications of behaviour which may arise in relation to some novel situation, hence with what is usually described as indicating intelligent as apart from instinctive acts, the former being not merely accompanied but controlled by consciousness (Lloyd Morgan).

In practical animal behaviour the two sets of processes are probably more or less constantly interwoven, the higher activities (supra-granular layer) coming to the aid of the lower as far as the capability of the animal allows. In the case of the lower mammals (*e.g.*, Insectivora) the limits of this capability are comparatively soon reached, and correspondingly these mammals possess a relatively poor supra-granular layer. Many of these lower mammals have adopted a safe mode of life, others have resorted to fecundity. With these, which may, for present purposes, be termed extraneous aids to survival, their essentially instinctive activities have been relatively sufficient to ensure their continued existence. There has, therefore, in these mammals, been little necessity for the development of a supra-granular layer, the infra-granular portion of the pallium providing most of the necessary cortical physical basis required for practical behaviour.

The infra-granular layers, with the reservation to which reference has been made, thus constitute the earlier developed and more fundamental associational system of the cerebral cortex; the supra-granular layer, a higher and accessory system super-added, and of any considerable functional importance only in certain regions in lower mammals, such as the Insectivora.

FURTHER CONCLUSIONS AS TO THE FUNCTIONAL SIGNIFICANCE OF THE CORTICAL AREAS IN THE INSECTIVORA.

In view particularly of the above thesis as to the functional significance of the cerebral cortical layers, attention may be directed to the following points concerning the cortical areas in the Insectivora examined in this series.

In the Hedgehog, in the area which is considered to possess visual functions, there is a moderately well developed (as regards individual cells) although thin supra-granular layer, which is practically absent in the comparatively blind Mole and Shrew in the corresponding region.

Further, in the area taken to represent the cortical distribution of the fifth sensory nerve there is in the Hedgehog a somewhat similar supra-granular layer to that found in the visual region, although rather better developed, whilst this layer is absent in the corresponding region in the Mole and Shrew. If this area has been correctly located the explanation of this difference in the supra-granular layer may be, that in the Mole and Shrew impressions through the fifth sensory nerve (superficial snout touch and vibrissæ sensations) are made use of by these tunnelling and run-making animals in a mechanical and instinctive, rather than in an intelligent manner, whilst in the roving and enterprising Hedgehog somewhat more intelligent use is made of such impressions.

Areas 1 and 2 in the Mole and Shrew, and the combined field in the Hedgehog, appear, in every sense, to be the most completely developed regions of neopallium which these animals possess, and are the only areas in the former

animals having a supra-granular layer of any considerable depth and complexity of component cell elements. In the two first-named animals, area 2, from its histological character, is believed to be concerned with the reception of sensory impressions; from its situation, and on account of the importance of kinæsthetic impressions in these animals, these impressions are probably largely kinæsthetic in nature. One would, therefore, also expect to find in this field, relative to the animals' cortical development in general, a good supra-granular layer.

With regard to area 1 in the Mole and Shrew, which has provisionally been termed "motor," its position, from the point of view of function, is a somewhat anomalous one if it is looked upon as merely a "Betz cell" area.* The area in question is, relatively to the size of the neopallium, a very large one as compared with that of the homologous area in mammals higher in the scale, *e.g.*, the Dog.

It seems necessary to assume that animals like the Mole are possessed of some means of simple sensory association, otherwise it is probable that the animal's waking life would tend to be one of almost continuous sensory confusion. Such association is called up by the stimulation of one or other or more than one special sense, and passes more or less directly to a motor or efferent result. This appears to be the lowest grade of conscious neopallial association—*i.e.*, of psychic function—and it doubtless persists in mammals much higher in the scale than the Insectivora, and possibly in the highest, though obscured in them by the development of a higher grade or grades. It is not likely to exist as a random passing to and fro of impulses from this sensory area to that, but to lie in some fusion zone. Careful examination of the cortex of animals like the Mole has failed to reveal any attempt at the develop-

* The term "Betz cell" area is used for convenience, and only in the sense that the large cells found in the fourth layer of the cortex in area 1 in the Mole are the probable origin of the efferent (motor) tracts, and are thus the probable analogues of the Betz cells found in the human cortex in the excito-motor area.

ment of a "psychic" zone in direct relation to any of the sensory projection spheres. The writer does not consider that on histological grounds one is justified in drawing close analogies between the areas he has termed "undifferentiated" in the Mole, &c., and the areas of cortex surrounding the projection spheres in certain higher mammals. From the histological aspect, therefore, the assumption that animals like the Mole possess any special areas of association, however small, appears to be unjustified, and there is also, in view of the following remarks, some reason for believing that such areas are in them physiologically unnecessary, in spite of the probable requirement by these animals of some physical basis for simple sensory association.

Dr. Bolton has suggested to the writer that in the Mole and similar animals the fusion zone for simple sensory impressions, *i.e.*, lowest grade of conscious association, lies in the area which has been designated "motor." Taking the Mole, for example, the areas mapped out as kinæsthetic, fifth sensory, visual, &c., are simple sensory reception spheres for the respective senses, whilst area 1 is the psychic equivalent of all these, and at the same time efferent. Area 1 would thus receive impulses from each or all of the sensory projection spheres and turn them into motor equivalents. It is a general area of simple sensory association with the origin of the efferent (motor) tracts included. This is as far as such an animal as the Mole has got in the direction of higher association. The structure of the cortex, however, even of this area, especially if regarded as being of an associational type, is of a relatively elementary nature.

The above suggestion does away with the apparent anomaly of the relatively great extent of area 1 if this be looked upon as nothing more than a "Betz cell" region. It also coincides with the fact that this area ranks with the best developed portion of the cortex as regards supragranular (pyramidal) layer which mammals such as the Mole possess, poor though this is.

The writer's views have been founded upon a study of

the cortex cerebri, not only in adult mammals but also in foetal and young animals. He concludes that in the cerebral cortex of many—and probably of all—adult lower mammals there are areas, considerable in extent, which throughout life advance little—as regards complexity of their component nerve cells—beyond their condition in the foetal or very young animal. It is, therefore, on histological grounds presumed that such areas are of comparatively little functional value to the animal.

He also considers it proved, as the result of the investigations of Bolton and himself, that the structure of the neopallium is founded upon an infra-granular basis. Further, it is suggested that in the earliest attempts at evolution of structure which come to be of any considerable functional value, the neopallium follows the plan of cortical architecture long previously in the phylogenetic scale laid down in the hippocampus, which plan in the latter situation has become fixed, and, as a plan, permanent. The earliest and lowest grade of neopallial representation is thus, as regards structure, a repetition of the hippocampal type—granular and infra-granular cortex. By the accrescence of a supra-granular layer of varying degrees of depth and complexity of its component nerve cells, different grades of representation may be reached, and are reached to some extent in the same animal, even if this occupies a lowly place in the mammalian phylum, and to a greater extent the higher is the position in the scale to which the animal belongs.

Applying these principles to the various grades of cortical structure seen either in the same or in different mammals the lowest grade may be illustrated by the cortex of the postero-mesial specialised area in the Mole. This represents the type of the simplest projection (sensory) sphere, consisting as it does almost only of granular and infra-granular portions of cortex. The structure of a more complex projection sphere is shown for example in the visual area of such Ungulates as the Pig or one of the Deer, where cortex exhibiting a deep granular layer is enriched by the addition of a very definite though relatively

shallow supra-granular layer. The most complex organisation shown by a projection sphere is found in the "visuo-sensory" area of a Primate—the oldest ontogenetically and the most definite as regards structure and localisation of all the Primate neopallial projection spheres. In this the cortex is characterised, as Bolton has shown, by a granular layer which has become hypertrophied and duplicated, whilst there is a considerable increase in depth of the supra-granular (pyramidal) layer, although the latter falls short by four-ninths of the depth of the corresponding layer in the surrounding "visuo-psychic" (associational) region. Taking mammals generally, in its organisation the simplest associational sphere, as contrasted with the simplest projection sphere, exhibits a diminished granular layer, and the addition of a distinct although not deep supra-granular layer. Such is illustrated by the cortex of the region designated area 1 in the Mole. Higher grades of associational type of cortex, with a further increase in depth and in complexity of the supra-granular layer, are feebly represented in the mammalian scale until the Primates are reached, but, as is well known, in the human subject a relatively very large amount of the neopallium consists of this type of cortex. As an example of the highest grade of associational cortex that of the human "visuo-psychic" area may be cited, this being characterised by a great increase in depth of the supra-granular layer as compared with the depth of this layer in the "visuo-sensory" region.

In mammals like the Insectivores the neopallium in certain regions shows "projection" cortex which is of the lowest grade, *i.e.*, possesses a structure which is practically of hippocampal type, and which, even in the better developed projection spheres in these animals, has advanced little beyond this, whilst attempts at the production of "association" cortex are, even in the best developed regions, of a simple and elementary nature.

This research was commenced systematically in the laboratory of the London County Asylums at Claybury, and the portion dealt with in the present paper was almost

completed in this laboratory. Some additions have been made in the laboratory attached to the Lancaster County Asylum at Rainhill. The writer may be permitted to express to the Pathological Sub-Committee of the London County Council and to Dr. Mott, also to the Committee of the Rainhill Asylum, and to Dr. Wigglesworth, his appreciation of the many facilities for research which have been afforded him.

To Dr. Mott, F.R.S., the writer is greatly indebted for much advice, and for an amount of encouragement without which the work could not have been undertaken at the time it was.

To Dr. Bolton's published work the writer trusts he has made sufficient acknowledgment throughout the paper. He also has to thank him for the micrometric measurements of the cortex of the Mole and for many suggestions. The writer must also express his indebtedness to the writings of Elliot Smith and Lloyd Morgan, an indebtedness which, particularly as regards the latter author, is of a general rather than of a specific nature.

To the Royal Zoological Society of London, and personally to Mr. Beddard, F.R.S., the writer is beholden for much of what may be spoken of in relation to the present paper as control material. For much of the actual material made use of he is indebted to Dr. Robert Jones, of Claybury, and Dr. J. H. Sproat, of Birmingham. A special word of thanks is due to Dr. Albert Wilson for the loan of many excellent and valuable preparations.

The photomicrographs were partly prepared at Rainhill and partly at Claybury, and the writer has to thank Mr. Abram, of Rainhill, and Mr. Geary, of the Claybury Laboratory, for much practical assistance in their production.

REFERENCES.

- ALLEN. *Journ. of Comp. Neurol. and Psych.*, vol. xiv., No. 4, 1904.
BOLTON. *Phil. Trans.*, Series B, vol. cxci. ; *Archives of Neurol.*, vol. ii., 1903 ; *Brain*, Part cii., Summer, 1903 ; *Journ. of Mental Science*, April, 1905, and April, 1906.

- CAMPBELL. "Histological Studies on the Localisation of Cerebral Function." Addendum, 1905.
- ELLIOT SMITH. *Journ. of Anat. and Phys.*, 1901, p. 431; "Catalogue of Roy. Coll. of Surg. Museum," Phys. Series, vol. ii.
- HERMANIDES AND KÖPPEN. *Archiv. f. Psych. u. Nervenkr.*, 1903, p. 616.
- MANN. *Journ. of Anat. and Phys.*, vol. xxx. (N. S., vol. x.), October, 1895.
- NISSL. *Münch. Med. Wochensch.*, Bd. xlv., 1898, S. 1027.
- WATSON. *Proc. Royal Soc., B.*, vol. lxxvii., 1905; *Archives of Neurol.*, vol. ii., 1903.

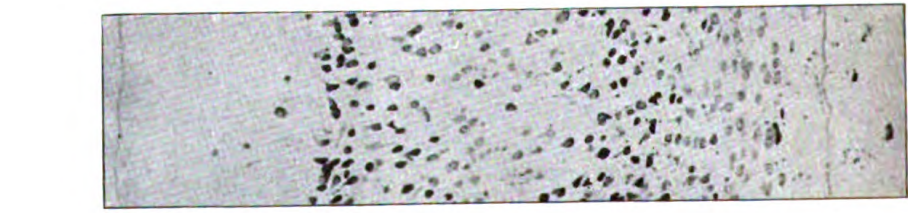
The photomicrographs 1 to 13 on Plates I. to IV. are all of the same magnification, viz., 125 diameters.

PLATE I.

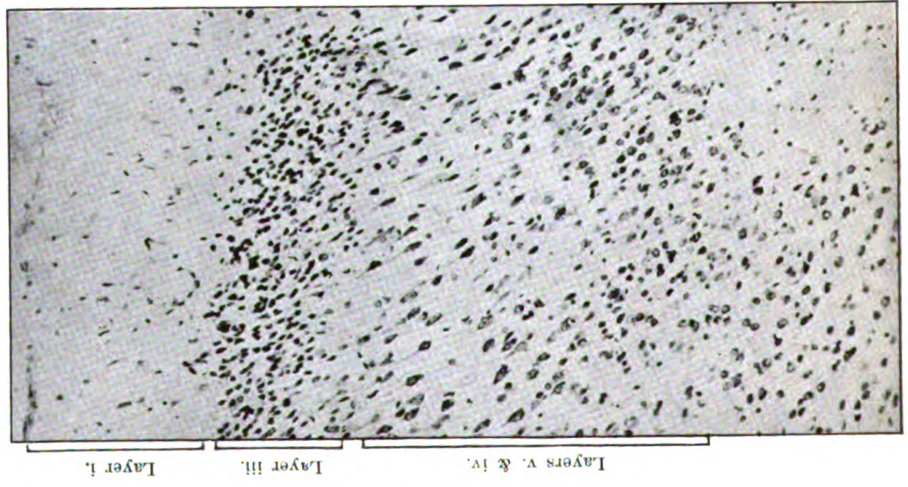
1. MOLE. The cortex of area 1, "Motor." In this, and others of the photomicrographs, the situation and depth of the several cortical layers is approximately indicated at the margin of the strip. There are, however, considerable variations in the depth of the cortical layers in different parts, even in the same area, and the general average depth of the layers as given on page 102 was obtained from a number of micrometric measurements.
2. MOLE. Area 2, "General Sensory," to the left with ending of this seen to the right and commencement of the "lateral area of undifferentiated cortex." In the sensory area the deep and definite granular layer (iii.) will be observed, also the few large cells in layer iv., as compared with the "motor" area. The abrupt ending of the granular layer as a definite lamina can be seen towards the right.
3. MOLE. Across furrow "b"—modified motor cortex becoming undifferentiated. The slight dipping of all the cortical layers in relation to the furrow can be seen, although this would be more clearly indicated were the strip wider. Owing to transparency the outer edge of the cortex has been slightly retouched. The other photomicrographs are all untouched.

UoM

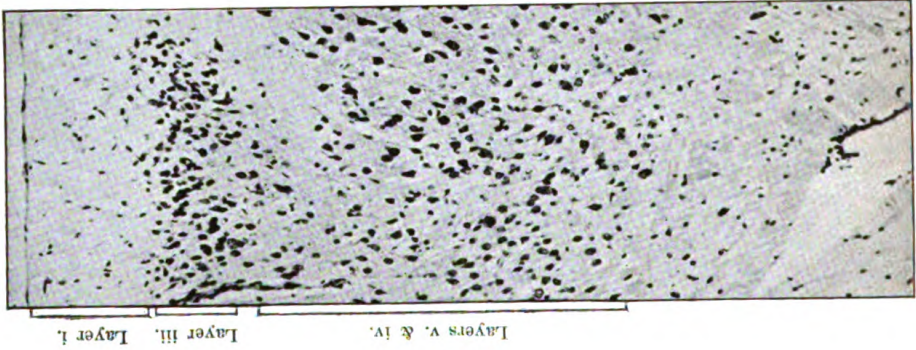
PLATE II.



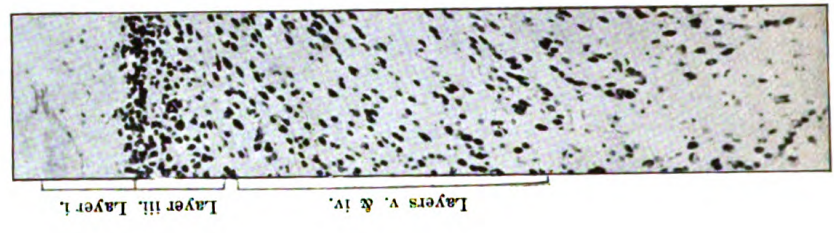
4 MOLE.
Face p. 119.



MOLE.



6. MOLE.



7. MOLE.

PLATE II.

4. Mole. Posterior area of undifferentiated cortex. Note the narrower cortex and the condition of the cellular elements, *e.g.*, as compared with the "Motor" area, Plate I., 1.

5, 6, 7. Mole. The three divisions of the postero-mesial area of specialised cortex as described in the text and figured on page 73.

5 (Division 1). The granular layer is very definite and prominent—its abrupt ending is seen towards the right. The infra-granular portion of the cortex is also well developed and contains numerous large cells. Special attention is directed to the practical absence of a supra-granular (pyramidal) layer in this as in the other divisions of this area of the cortex.

6 (Division 2). The cortex generally is less well developed than that of Division 1.

7 (Division 3). The cortex is rather better developed than that of Division 2, but is narrow, and the lamination is somewhat irregular. Owing to its obliquity in whatever direction the section is taken, this portion of the cortex is difficult to demonstrate in a narrow strip

PLATE III.

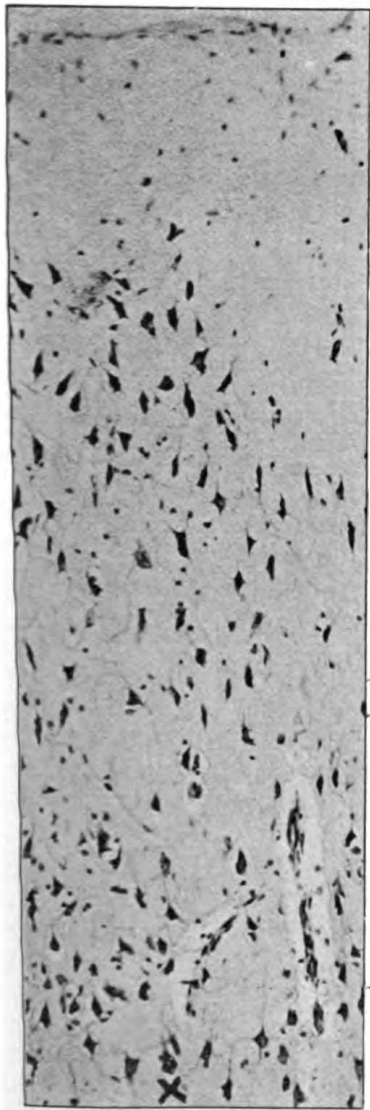
8. HEDGEHOG. "Sensory-motor" cortex in two strips; a X is placed beneath the same cell in each strip. The lamination will be observed to be more irregular than in the Mole and Shrew, and the several layers more difficult to delimit.

9. SHREW. "Motor."

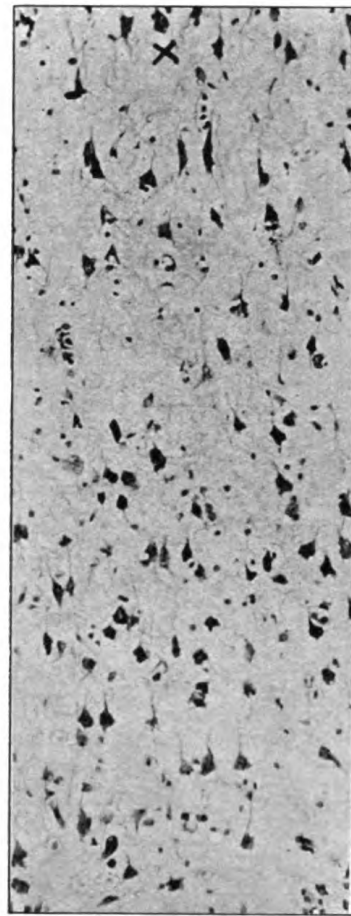
10. SHREW. "General sensory" cortex. Much the same distinctions between motor and sensory cortex are seen as in the Mole, the chief difference between the two, however, in the Shrew being in the increased depth and definiteness of the granular layer (iii.) in the sensory, as compared with the motor area.

Note the narrowness of the cortex; also how closely packed together are the individual cell elements and how small they are as compared especially with those of the Hedgehog.

PLATE III.

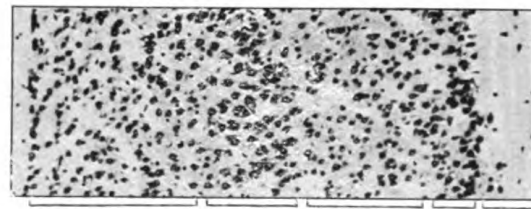


8. HEDGEHOG.



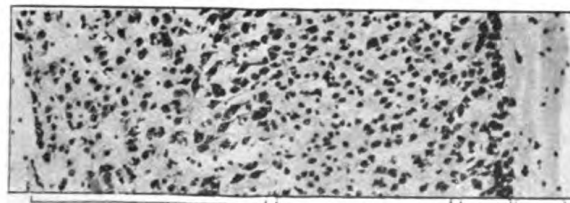
8. HEDGEHOG.

Layers iv. & v.



9. SHREW.

v. iv. iii. ii. i.

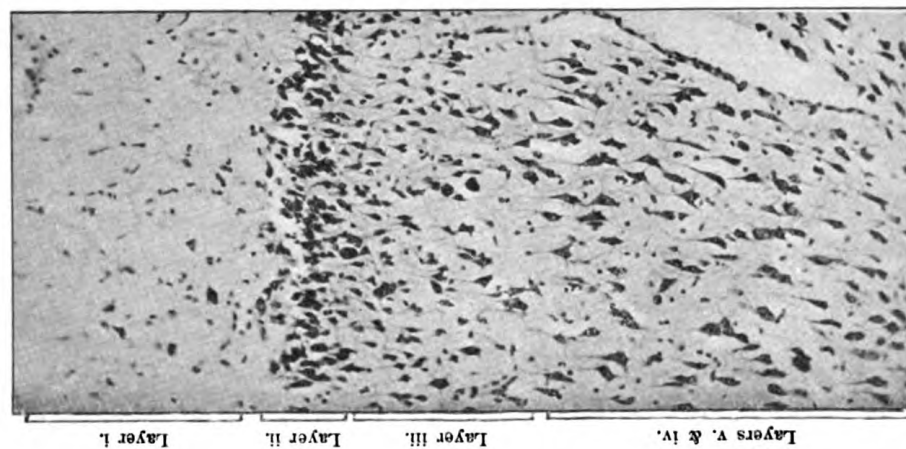


10. SHREW.

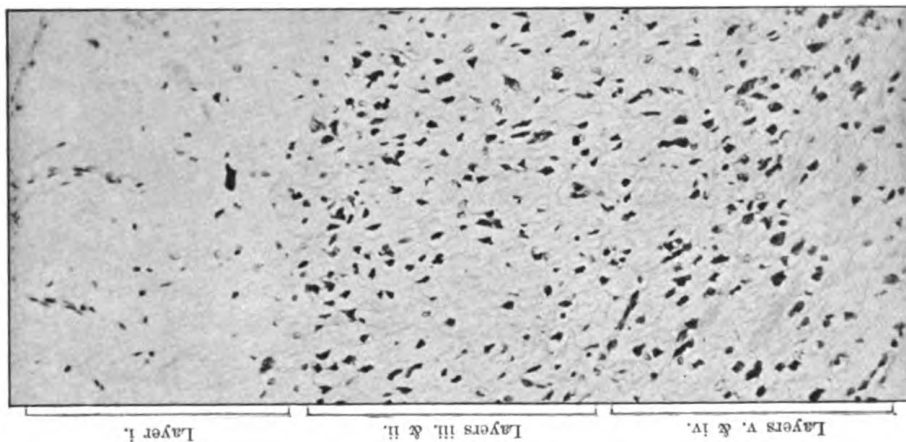
v. & iv. iii. ii. i.

1111

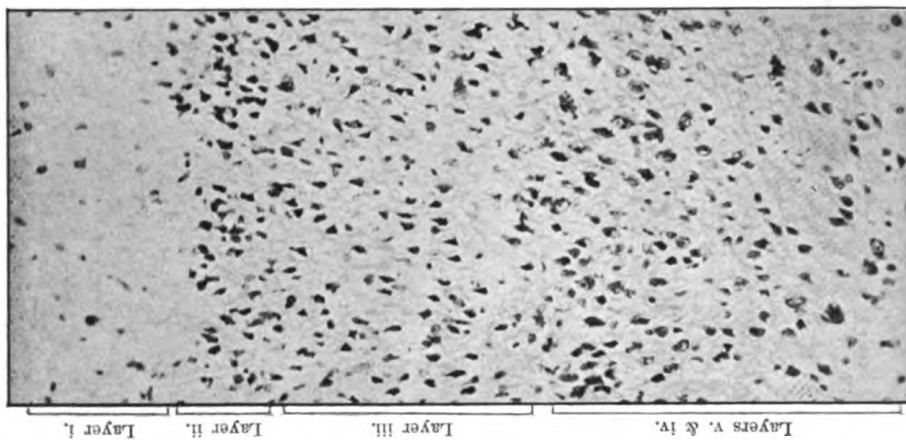
PLATE IV.



11. HEDGEHOG.



12. HEDGEHOG.



13. HEDGEHOG.

PLATE IV.

11, 12, 13. *HEDOGHO*. The three divisions of the postero-mesial area of specialised cortex as described in the text and figured on page 83. The whole of layer i. is not shown, except to the right in photomicrographs 11 and 12.

11 (Division 1). Note what is believed to be the representative of a shallow supra-granular layer (ii.), the definite granular layer (iii.), and the very well-developed infra-granular cortex (iv. and v.), containing numerous large well-formed cells.

12 (Division 2). The whole cortex is much less well developed than in Division 1, and the lamination is very irregular.

13 (Division 3). The cortex is better developed than in Division 2. There is a definite granular layer (cells rather spread out), and a well marked infra-granular cortex containing many large pale cells—the probable homologues of the solitary cells of Meynert.

PLATE V.

14. SHREW. Posterior portion of a longitudinal section of the hemisphere to show the relations of the postero-mesial area of specialised cortex (between the dotted lines). A X is placed at one end of the hippocampal formation. *Magnification 126 diameters.*

15 and 16. HEDGEHOG. Upper trisection of the sensori-motor cortex (15), and upper half of the postero-mesial "undifferentiated" cortex, omitting the greater part of the molecular layer (i.) in each instance; more highly magnified (viz , 157 diam.) than in the previous photomicrographs to show the different condition of the nerve cells in the two. See page 80 of text.

THE SUPRARENAL GLANDS IN NERVOUS AND OTHER DISEASES.

BY F. W. MOTT, M.D., F.R.S., AND W. D. HALLIBURTON, M.D.,
F.R.S.

ONE of us (F. W. M.), in a long experience of autopsies, performed chiefly at the London County Asylums, noticed how frequently the suprarenal or adrenal capsules appeared to be atrophied, soft or cystic, at the autopsy. This could hardly have been due to *post-mortem* changes, because at Claybury any extensive putrefactive changes are prevented by placing the bodies in a cold chamber, and the *post-mortem* examination is made usually within a few hours of death. It therefore appeared to be worthy of a more thorough investigation to see whether there is any constant relationship between wasting of the suprarenals and diseases of the nervous system. Such a connection is not on *a priori* grounds improbable, because the glands in question, so far as their medullary portions are concerned, are developed in close relationship to the sympathetic nervous system, and as Brodie and Dixon¹ were the first to prove, the action of adrenaline (the characteristic physiological material formed by the glands) is upon the sympathetic nerve endings. This conclusion was confirmed by Elliott.²

We have accordingly obtained from successive autopsies a large number of suprarenal glands, and subjected them to a more detailed examination. As will be seen from the tabular statement of results, the diseases dealt with are those commonly occurring in asylums, but, so far as could be ascertained, no case in which the sympathetic nervous system was specially involved came under our notice.

¹ *Journal of Physiology*, vol. xxx., p. 476. The idea was first suggested by Langley, *ibid.*, vol. xxvi., p. 237.

² *Ibid.*, vol. xxxii., p. 401. *British Medical Journal*, July 13, 1905.

At each autopsy a note was made of the naked eye appearances of the glands. On removal they were weighed separately. A portion of each was reserved for the purpose of trying Vulpian's well-known ferric chloride colour reaction for adrenaline, and another portion for microscopic investigation. The remainder was then rapidly dried *in vacuo*, powdered, and the proportion of water and solids determined. The dried powder was placed in well-stoppered tubes and labelled with a number. The appearance of the dried material differed very considerably; the majority were brownish in tint, and showed considerable admixture with fat; some few dried into a clean powder of tint varying from almost pure white to various shades of yellow and brown. This difference is probably accounted for by the difference in the amount of blood and of pigment in the glands. The powder was used for testing the physiological action of the glands.

We have here to acknowledge the help given by Mr. Sydney A. Mann, Assistant in the Pathological Laboratory, Claybury. The weighing and drying of the organs was carried out by him. He also performed the ferric chloride test with the fresh material, and prepared the microscopic sections. One of us (F. W. M.) is responsible for the report on the macroscopic and microscopic appearances shown, and the other (W. D. H.) for the physiological testing, which was carried out at King's College, London. It was not until both series of investigations were completed that the results were correlated, and the accompanying table drawn up.

THE METHODS ADOPTED IN THE PHYSIOLOGICAL TEST.

There are three principal physiological reactions which may be adopted for the detection of adrenaline. One of these is its dilating action in the pupil of the frog's eye (Meltzer)¹; this, however, was found not to be sufficiently delicate for our purpose.

¹ *American Journ. of Physiol.*, vol. xi., p. 449.

The second is the marked favouring result on the rate and strength of the beat of the isolated heart. This can be readily demonstrated on the isolated rabbit's heart, perfused according to Locke's method. This test is an exceedingly sensitive one; if adrenaline is added to the saline solution (Locke's modification of Ringer's solution) in the proportion of 1 in a million parts, the response is a marked one, and a good effect can frequently be obtained with a dilution equal to a tenth of that concentration. The disadvantage of the method is that with higher concentrations (and it was impossible to determine the concentration in our extracts) the after-effects on the heart-beat (irregularity and diminution of force) are so persistent that it is seldom possible to employ more than one test solution upon each heart. We, however, used the method in quite a number of extracts, and as the results always coincided with those obtained by the third method to be immediately described, we have in the main restricted ourselves to this third method.

This consists in injecting an extract of the powder intravascularly, and noting the rise of arterial blood pressure produced in an anæsthetised animal. The animals used were cats, and the anæsthetic A.C.E. mixture. The arterial pressure was registered by a mercurial manometer connected with the carotid artery, and the injection was made into the external jugular vein. Previous to the injection both vagi were out. The extracts were first made by boiling the dried powder with physiological salt solution in the proportions of 1 decigramme of the powder to 50 cc. of solution. But so many negative results were obtained with this strength that subsequently the proportion adopted was 4 decigrammes to 50 cc. of solution. It is possible that when only a decigramme was used, the portion of the powder used consisted mainly or wholly of the cortical part of the organ. This danger is minimised when more powder is employed: 10 cc. of the filtered extract at body temperature were used at each injection. Several injections were made of each extract, and the rise of blood pressure given in the tables is the

mean of all the experiments. In cases where a negative result was obtained, the experiment was usually tried on two animals, and in such cases, a negative result was not entered on our notes until the whole of the powdered gland was extracted, so that no particle of the medullary part of the gland might escape extraction.

There is no difficulty in performing several experiments on one animal; providing five or ten minutes elapse between the individual injections, no marked difference is noticeable between the results.

In each experiment two controls were performed: (1) The injection of the same volume (10 cc.) of salt solution. This if warmed to the body temperature produces no appreciable effect; (2) an injection of 2.5 cc. of solution of adrenaline chloride (1 in 100,000 of salt solution). This produces a rise of pressure which varies somewhat in different animals, but averages about 40 mm. of mercury. The rise produced by the injection of our extracts can be compared with this standard, and the several experiments, though they give one no idea of the quantity of adrenaline actually present, are comparable with each other. If any loss of the power of adrenaline by the processes of drying or boiling occurs, we take it that in a comparative method of this kind it will be approximately equal in all cases.

In cases where no rise of pressure occurs, and in which adrenaline may therefore be considered absent, a fall of pressure is the usual result. This is also the case for the extracts of the majority of other tissues.¹

THE FERRIC CHLORIDE REACTION.

This cannot be used quantitatively, and we have been obliged to have recourse to such adjectives as good, faint, &c., in describing the results.

MICROSCOPIC APPEARANCES.

In many cases the condition of the medullary and cortical portions of the organ showed little or no departure

¹ Vincent and Sheen, *Journ. of Physiology*, vol. xxix., p. 242.

from the normal. The amount of pigmentation of the medullary cells is very variable, but apparently this has but little relationship to physiological activity. At the other extreme there were cases where the medullary portion was atrophied, friable or cystic, and the cells in a degenerated state. This was in marked cases also recognisable by the naked eye. Between the two extremes there were cases where the glands presented but little naked-eye change, but the microscope revealed that the cytoplasm did not readily take the eosin stain: in these, as a rule, the physiological extract of the glands was weak.

In the tables that now follow, the age, sex and time of the autopsy after death are noted in each case. The disease for which the patient was in the asylum, and other diseases which complicated it, with the cause of death, are also given.

Next follow details about the glands themselves, their weight, the percentage of water in them, their microscopic and other appearances, and the intensity of the ferric chloride reaction.

The two last columns give the result of the injection of the extract on blood pressure compared with that produced by the small dose of adrenaline which was used as a control.

REMARKS ON THE TABLE.

The number of cases examined was seventy-one. This appeared to us sufficient, if any general deductions can be drawn. The deductions are, however, mainly of a negative character.

In the first place, it will be seen that the different series of observations fit together with remarkable accuracy. A negative or slight physiological effect on blood pressure coincides with a negative or feeble ferric chloride reaction, and with degenerative changes seen in the organs. To this rule there are so few exceptions that they may be explained by some accident impossible to trace now, but such as so frequently occur in a long series of observations carried out by different people. These exceptions are the following:—

No. 8.—Here the ferric chloride reaction was fairly good, and nothing very abnormal was seen in the glands; yet there was a negative effect on blood pressure.

Nos. 21, 22, 23 and 24.—Here the microscopic appearances are what one would expect to accompany the negative effect on blood pressure which was obtained. Nevertheless there was a good or fairly good ferric chloride reaction in each case. We think here that the greater reliance should be placed on the agreement rather than on the discrepancy.

Out of the total of seventy-one cases, the following twenty-three gave negative or practically negative effects:—

No. 1.—A case of dementia in a male aged 64, who had also chronic Bright's disease, and died from bronchō-pneumonia.

No. 4.—A case of melancholia in a female aged 51, who died of acute, supervening on chronic, phthisis.

No. 5.—A case of "weak-mindedness" in a male aged 46, who died from chronic phthisis.

No. 6.—A case of senile dementia in a male aged 65, who died from acute, supervening on chronic, phthisis.

No. 7.—A case of epilepsy and mania in a female aged 37, who died from an accident.

No. 9.—A case of general paralysis in a male aged 39, who died from chronic phthisis.

No. 10.—A case of chronic mania in a female aged 60, who died from chronic Bright's disease.

No. 12.—A case of dementia in a female aged 68, who suffered from a variety of complications (chronic Bright's disease, arterial degeneration, bronchitis and dysentery).

No. 18.—A case of alcoholic dementia and neuritis in a female aged 37, who had also tuberculous peritonitis and who died from dysentery.

No. 21.—A case of senile melancholia in a male aged 65, who died from pneumonia.

No. 22.—A case of melancholia in a male aged 56, who had also chronic Bright's disease with arterial degeneration, and who died from pneumonia.

No. 23.—A case of mania in a male aged 43, with similar complications.

No. 24.—A case of melancholia in a male aged 44, who had also arterial sclerosis, and died from cerebral hæmorrhage.

No. 26.—A case of senile melancholia in a female aged 83, who also had general arterial and renal sclerosis, and who died from pneumonia.

No. 27.—A case of general paralysis in a female aged 44, who had also carcinoma and died from broncho-pneumonia.

No. 28.—A case of general paralysis in a female aged 34, who had also phthisis and cancer.

No. 42.—A case of general imbecility and epilepsy in a female aged 46, who had also hypostatic congestion of the lungs and possibly myxœdema, and who died from cardiac failure.

No. 44.—A case of general paralysis in a male aged 42, who died from diphtheria and purulent bronchitis.

No. 46.—A case of senile dementia in a female aged 74, who had also chronic bronchitis, and died from broncho-pneumonia.

No. 56.—A case of delusional insanity in a female aged 63, who had also heart disease, renal cirrhosis and broncho-pneumonia and died from cardiac failure.

No. 60.—A case of mania in a female aged 43, who died from broncho pneumonia.

No. 63.—A case of senile mania in a female aged 78, who died from acute dysentery.

No. 68.—A case of senile dementia in a male aged 71, who had renal and general arterial sclerosis, and died from pneumonia.

In addition to these, there are the following twelve cases in which only slight evidence of the presence of adrenaline was obtainable, viz.:—

No. 10A.—Male, aged 42, general paralysis. Pneumonia and empyema.

No. 13.—Male, aged 60. Dementia ; acute dysentery.

No. 14.—Male, aged 37. General paralysis ; acute dysentery.

No. 15.—Male, aged 69. Senile melancholia ; acute dysentery.

No. 17.—Male, aged 38. Melancholia ; chronic Bright's disease and œdema of lungs.

No. 19.—Female, aged 37. General Paralysis ; nephritis ; dysentery.

No. 20.—Male, aged 49. Melancholia ; pneumonia.

No. 29.—Male, aged 49. Epileptic mania ; lympho-sarcoma.

No. 50.—Male, aged 46. Melancholia ; pneumonia.

No. 55.—Female, aged 75. Senile mania ; bronchitis and pneumonia.

No. 58.—Male, aged 36. Senile dementia ; pneumonia ; cardiac failure.

No. 69.—Male, aged 39. General paralysis ; congestion and œdema of lungs.

We have thus thirty-five cases out of seventy-one, or about one-half of the total, where adrenaline was either wholly absent, or present in diminished quantity.

No.	Sex	Age	Disease	Complications and cause of death	Autopsy, hours after death	ADRENALS			Ferric chloride reaction	Histological appearances	Result on blood pressure of injection of extract	Rise produced by adrenalin in same animal
						Weight		Water, per cent.				
						R.	L.					
1	M.	64	Dementia ..	Chronic Bright's disease and broncho-pneumonia	24	Gr. 14.9 gr.	Gr.	79.9	Very faint	Cystic degeneration of central portions of both glands	Fall ..	Mm. 40
2	F.	23	Mania ..	Phthisis ..	2	6.7	5.4	81.7	Good	Normal ..	Rise of 48 mm.	60
3	M.	67	Senile melancholia	Chronic Bright's bronchitis	1	4.55	4.55	74.1	Very good..	Normal ..	Rise of 62 mm.	40
4	F.	51	Melancholia	Acute, on chronic phthisis	5	4.87	4.65	71.8	Faint ..	Right medulla diminished, left normal	Fall ..	40
5	M.	46	Weak-mindedness	Chronic phthisis	11	6.02	4.27	80.2	Faint ..	Very little medulla left; tuberculous nodules in both glands	Fall ..	40
6	M.	65	Senile dementia	Acute, on chronic phthisis	11	4.47	4.2	65.4	Nil.	Medulla cystic and almost absent	Fall ..	40
7	F.	37	Epilepsy and mania	Choked by meat	23	3.55	3.3	69.8	Faint ..	Medulla much diminished upon right side	Fall; slight rise in one experiment = 2 mm.	40
8	M.	27	Melancholia	Atheroma; hypostatic congestion of lungs	25	7.12	3.85	79.4	Fairly good	Medulla congested; very little pigment in cells	Fall ..	48
9	M.	39	General paralysis	Chronic phthisis	16	4.12	4.85	74	Very faint	Fatty degeneration of cortex; medulla diminished	Fall ..	48
10	F.	60	Chronic mania	Chronic Bright's disease	9	3.29	3.6	80.3	Nil.	No eosinophile cytoplasm in medullary cells; cells disintegrated; pigment in cells of medulla	Fall ..	48

10A	M.	42	General para- lysis	Pneumonia and empyema	—	5.42	6.86	76.8	Fairly good	Cystic; medulla dimin- ished	Rise of 28 mm.	40
11	M.	76	Senile mania	Pleurisy; arterial degeneration	—	3.25	3.85	71.1	Good	Medulla diminished and friable	Rise of 60 mm.	40
12	F.	68	Dementia ..	Dysentery; chronic Bright's disease and bronchitis; advanced degen- eration of arteries	18	4.67	4.71	75.5	Nil.	Cells show cloudy swell- ing; medulla present in fair amount; cells do not stain well with eosin	Fall	—
13	M.	60	Dementia ..	Acute dysentery..	42	2.47	7.06	72	Very faint	Very friable; medulla much diminished; right organ very disintegrated	Rise of 18 mm.	44
14	M.	37	General para- lysis	Acute dysentery..	37	6.12	5.3	78.7	Fairly good	Nothing noteworthy ..	Rise of 23 mm.	44
15	M.	69	Senile melan- cholia	Acute dysentery..	12	3.05	3.82	78.1	Very faint	Medulla much dimin- ished and friable; cells do not stain well with eosin	Rise of 10 mm.	40
16	M.	32	General para- lysis	Phthisis; pneu- monia	30	3.05	2.33	77.5	Fairly good	Cortex pale; neither it nor medulla stain well; otherwise normal	Record lost ..	—
17	M.	38	Melancholia	Chronic Bright's disease; cedema of lungs	17	4.49	4.3	76.2	Faint	Medulla slightly dimin- ished, but normal	Rise of 14 mm.	40
18	F.	37	Alcoholic de- mentia and peripheral neuritis	Acute dysentery; tuberculous peri- tonitis	—	4.07	3.79	76.7	Nil.	Faint staining of cells throughout, otherwise structure fairly good; medulla very slightly diminished	Fall	38
19	F.	37	General para- lysis	Acute dysentery; acute suppur- ative nephritis	3	4.74	4.68	76	Fairly good	Medulla slightly dimin- ished; structure fairly normal	Rise of 10 mm.	38
20	M.	49	Melancholia	Lobar pneumonia	22	4.55	5.75	74.7	Very faint	Cystic; medulla greatly diminished, especially on right side; cells do not stain well	Rise of 2 mm.	38

No.	Sex	Age	Disease	Complications and cause of death	Autopsy. Hours after death	Adrenals				Ferric chloride reaction	Histological appearances	Result on blood pressure of injection of extract		Rise produced by adrenalin in same animal
						Weight		Water, per cent.	Fall ..			Rise of 30 mm.		
						R.	L.							
21	M.	65	Senile melancholia	Pneumonia; advanced arterial degeneration	42	Gr. 3.24	Gr. 3.82	73.1	Good	..	Very friable; medulla practically absent	Fall ..	..	Mm. 38
22	M.	56	Melancholia	Chronic Bright's disease; arterial degeneration; pneumonia	16	2.82	3.12	73.7	Fairly good		Friable; medulla practically absent; right more degenerated than left	Fall ..	..	38
23	M.	43	Mania	Chronic Bright's disease; broncho-pneumonia	4	4	3.62	70	Very good		Glands rather friable; medulla diminished; pigmented medullary cells not obvious	Fall ..	..	38
24	M.	44	Melancholia	Arterial sclerosis; cerebral hæmorrhage	8	3.75	—	73.5	Very good		Medulla greatly diminished, very friable; left too disintegrated to collect; medullary pigment obvious	Fall ..	..	38
25	F.	44	Mania	Phthisis; amyloid degeneration of liver, spleen and kidneys	12	4.44	3.5	79.8	Fairly good		Medulla slightly diminished; cells stain poorly but structure fair	Rise of 30 mm.		38
26	F.	83	Senile melancholia	General arterial and renal sclerosis; pneumonia	16	1.37	1.27	78.4	Nil.	..	Very small; medulla fibrous and diminished; cells of cortex and medulla stain well	Fall ..	..	75
27	F.	44	General paralysis	Carcinoma; broncho-pneumonia	13	7.88	5.24	79.6	Nil.	..	Secondary deposits of scirrhus cancer	Fall ..	..	75

28	F.	34	General para- lysis	Carcinoma; phthi- sis	23	4.54	3.88	78.7	Nil.	..	Cells unstainable and swollen; right has hæ- morrhages in medulla; no secondary growths in suprarenals	Fall ..	75
29	M.	49	Epileptic mania	Lympho-sarcoma in mediastinal glands, lungs and liver	6	8.2	10.97	69.9	Faint	..	Secondary deposits; little of normal gland sub- stance left	Rise of 32 mm.	42
30	M.	35	General para- lysis	Pneumonia and acute gastritis	8	5.17	5.92	75.6	Fairly good	..	Nothing noteworthy	Rise of 61 mm.	42
31	M.	54	Epileptic de- mentia	Tuberculosis of lungs	4	3.78	3.64	79.1	Very good	..	Normal ..	Material lost	
32	M.	33	General para- lysis	Double lobar pneu- monia	13	5.05	6.44	75.9	Fairly good	..	Practically normal	Rise of 52 mm.	42
33	M.	66	General para- lysis	Hypostatic pneu- monia	5	3.74	5.57	70.9	Very good	..	Practically normal	Rise of 42 mm.	42
34	M.	44	General para- lysis	Acute colitis and gastritis	4	4.79	4.85	73.4	Fairly good	..	Practically normal	Rise of 24 mm.	42
35	Material lost.												
36	M.	47	General para- lysis	Hypostatic conges- tion and oedema of lungs; arterial sclerosis	23	6.38	6.07	67.9	Fairly good	..	Practically normal; me- dulla slightly dimin- ished	Rise of 16 mm.	42
37	F.	48	Melancholia	Embolism of left internal carotid	18	4.17	4.55	77.2	Good	..	Practically normal; me- dulla slightly diminished	Rise of 20 mm.	42
38	M.	62	Senile demen- tia	Acute dysentery; broncho-pneu- monia	7	4.17	4.52	71.5	Fairly good	..	Excess of fibrous tissue; medulla diminished	Rise of 22 mm.	42
39	M.	55	General para- lysis	Acute dysentery..	18	5.5	5.4	78.0	Very good	..	Some disintegration of medulla	Rise of 50 mm.	24
40	M.	35	General para- lysis	Fibrosis of organs; broncho-pneu- monia	4	5.77	5.27	77.2	Faint	..	Practically normal	Rise of 12 mm.	24
41	M.	61	General para- lysis	Hypostatic pneu- monia		4.16	5.07	73.9	Fairly good	..	Medulla diminished	Rise of 38 mm.	24

No.	Sex	Age	Disease	Complications and cause of death	Autopsy. Hours after death	Adrenals				Ferric chloride reaction	Histological appearances	Result on blood pressure of injection of extract	Rise produced by adrenalin in same animal
						Weight		Water, per cent.					
						R.	L.						
						Gr.	Gr.						Mm.
42	F.	46	Congenital imbecility and epilepsy	Cardiac failure; hypostatic congestion and oedema of lungs; myxœdema?	7	2.83	3.27	71.2	Nil.	..	Hæmorrhage in cortex and medulla, but little of the gland substance left	Fall	24
43	M.	36	Epileptic dementia	Hypostatic pneumonia; epileptic seizures; local cerebral softenings	42	3.09	2.73	71.6	Very good	..	Cytoplasm pale, and not much pigment on medulla, otherwise good	Rise of 30 mm.	24
44	M.	42	General paralysis	Diphtheria; purulent bronchitis	30	2.62	5.15	73.4	Faint	..	Cells of cortex and medulla faintly stained and vacuolated; abundance of pigment in medullary cells	Fall	30
45	M.	41	General paralysis	Lobar pneumonia; fibrosis of organs	4	3.77	3.38	70.9	Faint	..	Cells of cortex and medulla faintly stained and vacuolated; abundance of pigment in medullary cells	Rise of 40 mm.	30
46	F.	74	Senile dementia	Chronic bronchitis and emphysema; broncho - pneumonia	17	3.3	4.02	71.4	Nil.	..	Similar to No. 45, only more marked; in places the pigment alone is all that is left of the medullary cells	Fall	30
47	F.	35	Dementia ..	Purulent bronchitis; broncho-pneumonia; morbus cordis	46	4.21	3.16	76.6	Fairly good	..	Cells stain well, especially in patches	Rise of 20 mm.	30

48	M.	47	General paralysis	Gangrene of lung; aneurism of aorta	12	5.49	3.66	81.2	Fairly good	Somewhat congested, otherwise normal; cells stain readily, and show marked pigmentation	Rise of 56 mm.	30
49	M.	61	General paralysis	Exhaustion of general paralysis; fibrosis of organs	8	3.15	3.24	70.7	Very good	Islets of well-stained cells among others not so well stained; medulla shows good pigmentation	Rise of 60 mm.	30
50	M.	46	Melancholia	Lobar pneumonia	2	3.37	3.57	75.4	Fairly good	Much the same as No. 49	Slight fall ..	30
51	M.	73	Mania	Chronic bronchitis and emphysema; hypostatic pneumonia; renal cirrhosis	10	4.47	2.39	76.5	Good	Much the same as Nos. 49 and 50	Rise of 82 mm.	70
52	M.	62	Early general paralysis	Cardiac failure; acute pericarditis	5	3.35	1.20*	68.9	Good	Much the same as Nos. 49 and 50.	Rise of 60 mm.	70
53	F.	70	Senile mania	Acute dysentery; acute vegetative endocarditis	8	3.05	3.68	72.3	Faint	Left cortex cells well stained; medulla good with pigmented cells in abundance; right not quite so good	Rise of 42 mm.	70
54	F.	67	Senile mania	Emphysema of lungs and chronic bronchitis; cardiac failure	12	5.18	5.22	77.2	Fairly good	Cortex and medulla both good, especially right	Rise of 76 mm.	70
55	F.	75	Senile mania	Hypostatic pneumonia; chronic bronchitis and emphysema	23	3.65	3.06	72.4	Nil.	Cortex well stained in parts; medulla diminished, no obvious pigmented cells; a good deal of leucocytic infiltration	Rise of 8 mm.	70

* Only about half an organ recovered.

No.	Sex	Age	Disease	Complications and cause of death	Autopsy. Hours after death	Adrenals				Ferric chloride reaction	Histological appearances	Result on blood pressure of injection of extract	Rise produced by adrenalin in same animal
						Weight		Water, per cent.					
						R.	L.						
						Gr.	Gr.						Mm.
56	F.	63	Delusional insanity	Cardiac failure; hypostatic pneumonia, renal cirrhosis, heart disease	21	3.67	4.20	71.0	Very faint	Cells of both cortex and medulla stain faintly; medulla well pigmented	Fall	44	
57	F.	37	General paralysis	Purulent bronchitis, broncho-pneumonia; chronic tuberculosis of lungs	6	5.56	4.03	73.8	Fairly good	Gland structure good, but a large proportion of cells stain badly; no obvious pigmentation in medulla	Rise of 42 mm.	44	
58	M.	36	Senile dementia	Cardiac failure; hypostatic pneumonia	24	5.12	4.25	71.9	Faint ..	Glands wasted; otherwise like No. 57	Rise of 10 mm.	24	
59	F.	70	Senile melancholia	Dysentery; senile decay; bronchitis and emphysema	5	4.67	3.21	74.5	Fairly good	Gland structure good and cells mostly stain well; pigment in cells of medulla	Rise of 60 mm.	24	
60	F.	43	Mania	Acute bronchitis and broncho-pneumonia	8	—	4.50	70.3	Very faint	Hardly any cell of cortex or medulla stains	Fall	24	
61	F.	74	Senile mania	Acute dysentery; chronic bronchitis and emphysema	22	2.98	2.42	76.6	Fairly good	Cells stain well	Rise of 30 mm.	24	
62	M.	66	Senile dementia	Lobar pneumonia; chronic Bright's disease	26	4.77	8.62	69.6	Faint ..	Right shows very little medullary substance; left excess	Rise of 20 mm.	24	

63	F.	78	Senile mania	Acute dysentery..	25	5.37	4.45	77.6	Faint	..	Much breaking up of the large pigmented medullary cells; in some parts the cells are absent, and replaced by homogeneous matter	Fall	34
64	M.	34	General paralysis	Acute dysentery..	6	5.92	5.93	74.1	Good	..	Some breaking up of medullary cells; otherwise good	Rise of 40 mm.	34
65	M.	43	General paralysis	Cardiac failure; cardiac dilatation	3	3.81	3.49	67.2	Good	..	Cortex good; medullary substance poor	Rise of 50 mm.	30
66	F.	53	General paralysis	Tuberculosis of lungs; fibrosis of organs	6	4.72	4.96	68.7	Faint	..	Not much pigment in medulla	Rise of 28 mm.	30
67	F.	42	General paralysis	Purulent bronchitis and bronchopneumonia	19	3.84	4.66	78.2	Faint	..	Central substance not very good; fibrous all through	Rise of 34 mm.	30
68	M.	71	Senile dementia	Lobar pneumonia; general arterial degeneration; renal cirrhosis	8	4.1	4.62	72.1	Nil.	..	Medullary substance poor	Fall	30
69	M.	39	General paralysis	Hypostatic congestion and oedema of lungs	42	5.02	5.58	73.0	Faint	..	Very few pigmented cells in medulla; cells much replaced by transparent material	Rise of 8 mm.	42
70	M.	28	Mania	Broncho-pneumonia; gangrene of lung	46	5.70	4.65	78.6	Fairly good	..	Cystic; central cells well pigmented	Rise of 36 mm.	42
71	F.	65	Senile dementia	Bronchitis and broncho-pneumonia	19	4.09	5.06	76.7	Good	..	Good; cells well pigmented	Rise of 40 mm.	42

Out of these there are comparatively few cases where the lack of secretion was due to gross lesions. These few are the following :—

- No. 5.—Tuberculous nodules present.
- No. 6.—Medulla cystic.
- No. 20.—Medulla cystic.
- No. 21.—Medulla practically absent.
- No. 22.—Medulla practically absent.
- No. 24.—Medulla disintegrated.
- No. 27.—Secondary deposits of cancer present.
- No. 42.—Extensive hæmorrhage present.

In the majority of remaining negative or poor results, the note frequently occurs that the medulla was diminished, or the cells present a degenerated appearance. The most constant feature is the poor staining of the cytoplasm with eosin.

If these cases are compared with those that gave a positive result, it will be seen that sometimes the cells presented similar, though, as a rule, less marked, changes, and the changes frequently are seen in islets of cells, the surrounding cells staining well. In one or two positive cases, the medulla, though cystic, nevertheless gave good evidence of the presence of adrenaline.

Before proceeding to compare more fully the two classes of results, we may briefly tabulate the diseases from which the patients suffered, in the cases that gave a positive result. These are as follows :—

- No. 2.—Female, aged 23. Mania ; phthisis.
- No. 3.—Male, aged 67. Senile melancholia ; chronic Bright's disease and phthisis.
- No. 11.—Male, aged 76. Senile mania ; arterial degeneration ; pleurisy.
- No. 16.—Male, aged 32. General paralysis ; phthisis and pneumonia.
- No. 25.—Female, aged 44. Mania ; phthisis ; amyloid degeneration.
- No. 30.—Male, aged 35. General paralysis ; pneumonia and acute gastritis.
- No. 31.—Male, aged 54. Epileptic dementia ; tuberculosis of lungs.
- No. 32.—Male, aged 33. General paralysis ; double pneumonia.
- No. 33.—Male, aged 66. General paralysis ; pneumonia.

- No. 34.—Male, aged 44. General paralysis ; acute colitis.
 No. 36.—Male, aged 47. General paralysis ; congestion and œdema of lungs.
 No. 37.—Female, aged 48. Melancholia ; cerebral embolism.
 No. 38.—Male, aged 62. Senile dementia ; acute dysentery.
 No. 39.—Male, aged 55. General paralysis ; acute dysentery.
 No. 40.—Male, aged 35. General paralysis ; broncho-pneumonia.
 No. 41.—Male, aged 61. General paralysis ; pneumonia.
 No. 43.—Male, aged 36. Epileptic dementia ; pneumonia.
 No. 45.—Male, aged 45. General paralysis ; pneumonia.
 No. 47.—Female, aged 35. Dementia ; purulent bronchitis and pneumonia.
 No. 48.—Male, aged 47. General paralysis ; gangrene of lung.
 No. 49.—Male, aged 61. General paralysis ; fibrosis ; exhaustion.
 No. 51.—Male, aged 73. Mania ; chronic bronchitis ; hypostatic pneumonia.
 No. 52.—Male, aged 62. Early general paralysis ; acute pericarditis.
 No. 53.—Female, aged 70. Senile mania ; acute dysentery.
 No. 54.—Female, aged 67. Senile mania ; bronchitis ; cardiac failure.
 No. 57.—Female, aged 37. General paralysis ; purulent broncho-pneumonia.
 No. 59.—Female, aged 70. Senile melancholia ; dysentery.
 No. 61.—Female, aged 74. Senile mania ; acute dysentery.
 No. 62.—Male, aged 66. Senile dementia ; pneumonia.
 No. 64.—Male, aged 34. General paralysis ; acute dysentery.
 No. 65.—Male, aged 43. General paralysis ; cardiac failure.
 No. 66.—Female, aged 53. General paralysis ; tuberculosis of lungs.
 No. 67.—Female, aged 42. General paralysis ; purulent broncho-pneumonia.
 No. 70.—Male, aged 28. Mania ; broncho-pneumonia and gangrene of lung.
 No. 71.—Female, aged 65. Senile dementia ; broncho-pneumonia.

It is quite evident, from a comparison of these lists, that the original complaint for which the patient was admitted into the Asylum has no relationship to the condition of the suprarenals, also that age and sex are factors that have no influence.

It is, however, interesting to see whether a determining

factor may be found in the supervening disease and cause of death.

The summary presented enables us to classify these diseases into two main divisions, namely, those which are acute, like pneumonia and dysentery, and those which are chronic, like phthisis, cancer, or Bright's disease.

Out of the twenty-three cases in which the suprarenals gave negative results, the following seventeen died after a chronic disease, although in some cases they were ultimately carried off by an acute disorder: Nos. 1 (Bright's disease), 4 (phthisis), 5 (phthisis), 6 (phthisis), 9 (phthisis), 10 (Bright's disease), 12 (Bright's disease), 18 (tuberculosis), 22 (Bright's disease), 23 (Bright's disease), 26 (arterial and renal sclerosis), 27 (cancer), 28 (phthisis and cancer), 42 (probably myxœdema), 46 (chronic bronchitis), 56 (renal cirrhosis), 68 (renal and arterial sclerosis).

Out of the twelve cases where slight evidence of the presence of adrenaline was forthcoming, the death was nearly always due to an acute cause, like pneumonia or dysentery, and chronic previous ailments are only mentioned in four cases, viz.: Nos. 17 (Bright's disease), 29 (lympho-sarcoma), 55 (chronic bronchitis), and 69 (pulmonary œdema).

Out of the thirty-five cases in which a good positive result was obtained, again the usual cause of death was an acute illness, and chronic illness is only mentioned in the following nine cases, viz.: Nos. 2 (phthisis), 3 (Bright's disease and phthisis), 11 (arterial degeneration), 16 (phthisis), 25 (phthisis and amyloid degeneration), 31 (phthisis), 49 (exhaustion and general fibrosis), 51 (chronic bronchitis), and 66 (phthisis).

The records of the patients kept during their residence in the Asylum are, unfortunately, not in all cases sufficiently full to enable us to follow more accurately the course of the diseases; for instance, to distinguish, in cases of phthisis, which were acute and which chronic. In such cases, the only guide to the duration of the bodily disease was that afforded by the results of the autopsy.

But even as the tables stand, they show that 74 per cent

of the cases which gave a negative result suffered from long-continued and exhausting disease; whereas in those cases which gave a positive result, the same may be said concerning only 28 per cent.

We may therefore conclude that severe illness, especially if prolonged and chronic, impairs the secretory activity of the suprarenal gland, as it does that of numerous other secreting organs of the body; that inactivity, and even wasting and degeneration in the suprarenal may supervene in many of such ailments, and that Addison's disease is not the only one in which a defect in the suprarenal mechanism may occur.

We are confirmed in this opinion by the examination of a few specimens of suprarenals removed from hospital cases; in two surgical cases, for instance, even although the autopsy was made nearly three days after death, there was still evidence of the presence of adrenaline; whereas in two medical cases, one of cancer, the other of phthisis, adrenaline was absent in the first, and almost so in the second case. In all four cases the glands themselves presented no obvious abnormalities.

Acute disease, however, if sufficiently severe, is able sometimes to depress the suprarenal function in a corresponding way, as a glance through the tables will show. When one of us (W. D. H.) was in South Africa in 1905, this aspect of the question was brought prominently forward. Dr. D. T. Hoskyn, of H.M.S. "Crescent," communicated by letter some interesting facts to the meeting of the British Association at Johannesburg, in relation to cases of plague under the care of Dr. Barcroft Anderson, of East London, Cape Colony. In this extremely severe disease, the suprarenals are nearly always shrivelled and sometimes softened. This he attributed to too great a strain being placed upon the suprarenal bodies while endeavouring to counteract the plague poison, which is, among other things, a vaso-paralyser. He further found that the administration of adrenaline is beneficial in plague. But as this method of treatment is only at present in the experimental stage, it is too early to say whether the theory

suggested is correct. The fact of suprarenal atrophy in plague, however, supports our view that these glands suffer with the rest of the body in any depressing pathological condition. It may even be that the loss of the secretion may contribute to the vascular exhaustion which culminates in death. The possibility is also suggested that the fatal termination of chronic diseases is accelerated by the lack of suprarenal secretion and the consequent circulatory depression.

The tables illustrate one more series of observations, namely, those on the weight and percentage of water in the suprarenals. It will be noticed how very variable both these sets of numbers are, but the variations do not seem to be correlated with the other factors in our cases in any way.

GENERAL CONCLUSIONS.

(1) Atrophy and degenerative changes in the suprarenal glands are frequent in the class of nervous diseases (asylum cases) which we have specially investigated.

(2) These changes, however, do not appear to be related in any special way to the kind of disease for which the patients were admitted to the asylums.

(3) They appear rather to be the consequence of the secondary diseases which ultimately caused death.

(4) The suprarenal glands, like other secreting glands, are adversely affected by any disease which impairs the general nutrition of the body.

(5) The diseases which appear to be specially efficacious in producing this result are those of a chronic and wasting nature, but acute disease, if sufficiently intense, will often produce the same result.

ON THE CONDITION OF THE BLOOD IN
GENERAL PARALYSIS OF THE INSANE,
WITH SPECIAL REFERENCE TO THE CON-
DITION OF THE WHITE CELLS.

BY ARTHUR E. BODINGTON, M.A., M.D.CANTAB.

*Late Assistant Medical Officer, Cane Hill Asylum, and West Riding
Asylum, Wakefield.*

SEVERAL observers have drawn attention to the condition of the blood in general paralysis of the insane. Sutherland¹ found a leucocytosis in general paralysis. Macphail² notes a decrease in the number of red cells and in the percentage of hæmoglobin with an increase in the number of white cells. Bevan-Lewis³ found a diminution of hæmoglobin in all cases of general paralysis examined by him, and a diminution in the colorimetric power of the corpuscles. He says: "Taking into consideration the corpuscular richness, we find that the absolute deficiency of hæmoglobin gives a corpuscular value varying between 56 and 89 per cent."

Both Bevan-Lewis and Macphail draw attention to the sluggish flow of the blood in certain cases of general paralysis, notably in the third stage of the disease.

Capps,⁴ in a lengthy essay on the subject, comes to the following general conclusions:—

That the percentage of hæmoglobin and number of red cells are always diminished and that the specific gravity of the blood falls slightly below the normal.

"That most cases show a slight leucocytosis amounting on an average to about 22 per cent. above the normal,

¹ *Proceedings of the Royal Medical and Chirurgical Society*, April, 1873.

² *Journal of Mental Science*, 1884, vol. xxxi., p. 378.

³ "Text-book of Mental Diseases," 1889, p. 287.

⁴ *American Journal of the Medical Sciences*, 1896, iii., p. 650.

while in the differential count of these white cells a decrease is found in the lymphocytes along with a marked increase in the large mononuclear cells.

"Eosinophils are occasionally numerous. There is a leucocytosis after convulsions and apoplectic attacks which is as sudden as it is usually pronounced. It certainly does not appear until within a short time preceding the convulsion, probably not before it actually takes place.

"The degree of leucocytosis and the period of its continuance as a rule vary directly with the length and severity of the attack, and in the production of the leucocytosis, the large mononuclear cells are increased relatively more than any other variety."

Howard Green¹ examined some cases at Claybury Asylum, and found the percentage of hæmoglobin to be almost invariably reduced, and that occasionally the number of red cells per cubic millimetre was very high (in one case, 5,977,000).

SCOPE OF INVESTIGATION.

The present research is directed chiefly towards determining the number and variety of the white cells in the blood in general paralysis as seen in asylum practice, that is, during the second and third stages of the disease.

- (a) At different phases of the disease.
- (b) At different periods of the day.
- (c) During and following convulsive seizures and epileptiform attacks.

The following additional data were also ascertained :—

The specific gravity of the blood.

The blood pressure.

The percentage of hæmoglobin.

The number of red corpuscles.

The red cell index.

These latter observations were made in some cases daily, in other cases twice a day during the second and third stages of the disease.

¹ "Archives of Neurology from the Pathological Laboratory of the London County Asylum," 1899, p. 204.

METHODS.

The number of red and white cells was determined by means of the Thoma-Zeiss hæmocytometer, the blood in all instances being taken, without pressure, from the lobe of the ear.

In the case of the red corpuscles 200 squares were counted, and the results repeatedly checked by a second or third enumeration, in each case from a fresh drop of blood.

In the case of the white cells 400 squares were counted and checked in like manner.

The method of film staining (after fixation by formalin vapour) described by the Hon. G. Scott¹ was used for differential counting. This method is easy to use, rapid, and the results obtained uniform; the different varieties of cell easily seen and distinguished, so that the wearisome process of counting a large number of cells is made as little fatiguing as possible.

In the differential counts of the white cells the percentages were calculated from a total of not less than 500 cells, in many cases over 1,000 being enumerated, one-half of these on each cover-glass used in making the blood film.

The classification of the white cells used is that of Kanthack and Hardy:—²

- (1) Finely granular oxyphils.
- (2) Coarsely granular oxyphils. Eosinophils.
- (3) Lymphocytes. Small mononuclear cells with scanty protoplasm.
- (4) Hyaline. Large mononuclear cells with abundant clear protoplasm.
- (5) Basophil.

The specific gravity was determined by Hammerschlag's modification of Roy's method as described by Cabot.³

The blood pressure was estimated by means of Oliver's gauge, but this proved an unsatisfactory instrument, in our

¹ *Journal of Pathology and Bacteriology*, 1901, vol. vii. p. 131.

² *Journal of Physiology*, 1894, vol. xvii., p. 81.

³ Cabot, "Clinical Examination of the Blood," 1897, p. 29.

hands, in these cases, muscular tremor being so common in the latter stage of the disease as to make it often impossible to obtain reliable readings.

Von Fleischl's hæmoglobinometer was used to determine the percentage of hæmoglobin, three or four observations being made and the average recorded, the light used being constant (the flame of a single candle in a dark room at a constant distance).

The subjects chosen for examination were asylum patients showing signs and symptoms of general paralysis, care being taken, in so far as it was possible, to exclude from examination, all cases suffering from other diseases, such as phthisis, pneumonia, cystitis, bedsores, and septic diseases.

Such patients belong to the second and third stage of the disease, opportunities for seeing quite early cases in asylum practice being very few.

The body temperature of the patients during these examinations was, with one exception, within normal limits. Special reference will be drawn to this case in discussing Table IV.

The method of examination employed having now been described, we pass on to consider in detail the various results obtained under the separate headings on page 144, in which order they will be described.

DIFFERENTIAL COUNTS OF THE WHITE CELLS.

(a) *At different phases of the disease.*—On looking over Tables I. and II., which are drawn up from the differential counts of the white cells in a number of cases of general paralysis, it will be seen that the relative proportion of the cells varies within wide limits.

If we take the average count of the cases in the third stage, Table I., and compare it with the average of the twelve cases in the early second stage in Table II., we find a contrast as marked as that of the physical condition of the patients themselves.

These averages are :—

	Finely granular oxyphils		Coarsely granular oxyphils		Lymphocytes		Hyaline	
In third stage ..	80.9	..	..	1.1	..	8.8	..	8.3
In second stage ..	57.9	..	..	2.6	..	25.5	..	13.8

It is obvious, therefore, that while in the third stage the finely granular oxyphil cells are much above the normal in health and the mono-nuclear cells much reduced, in the second stage the reverse condition obtains, viz., there is a fall in the percentage of the finely granular oxyphils and a corresponding rise in that of the mono-nuclear cells.¹ The extreme cases, as indicated by the finely granular oxyphils, being respectively :—

	Finely granular oxyphils		Coarsely granular oxyphils		Lymphocytes		Hyaline	
In third stage ..	85	..	..	.6	..	6	..	7
In second stage ..	37.5	..	..	7	..	30	..	25.3

Of the mono-nuclear cells, moreover, the normal proportion of hyaline cells to lymphocytes is disturbed, the former in the third stage equalling, or even exceeding in number, the latter variety.

In the second stage, of the total increase in the mono-nuclear forms, hyaline cells are much more proportionately numerous than the lymphocytes, forming, indeed, occasionally 20 per cent., and in one case 25.3 per cent., of the total white cells.

The coarsely granular oxyphils, *i.e.*, eosinophils, are as a rule more numerous in the second stage, amounting in some cases to 6 and 7 per cent. Of other varieties a few transitional forms are seen and a few coarsely granular cells with large single nucleus staining faintly, and containing large conspicuous granules "which take a modified basic colour," Mast cells.² They are, as a rule, most numerous when the coarsely granular oxyphil cells are abundant.

Occasionally, a few large myelocytes are to be found in

¹ While Capps notes a leucocytosis in most stages of this disease, he adds that nothing further can be said with regard to a correspondence between the degree of leucocytosis and the stage of the disease. We would here, however, point out this very marked difference in the *character* of the white cells.

² Da Costa, "Clinical Hæmatology," 1902, Plate II., 33, 34.

the blood in these cases. We shall have occasion to refer to these, however, in dealing with the conditions found during convulsive seizures.

That this is no casual difference between the two stages of the disease, but that it is maintained from day to day, will be made clear on consulting Tables III. and V., and Tables VI. and VII., the two former showing daily counts in the third stage, the two latter in the second stages, for periods varying from eleven to twenty days. The averages obtained from Tables III. and V., and from Tables VI. and VII., respectively, are :—

Tables	Finely granular oxyphils	Coarsely granular oxyphils	Lymphocytes	Hyaline
III., V. ..	.. 78.1 ..	.. .9 ..	.. 14.3 ..	.. 6.2
VI., VII.	.. 64.5 ..	.. 2.5 ..	.. 22.9 ..	.. 9.6

These results harmonise with those obtained from the preceding three tables, the contrast between the two stages being distinct.

I have not included Table IV. in these averages, for the reason that during the period in which the examinations were made this patient was subject to rises of temperature above the normal. The average, however :—

Finely granular oxyphils	Coarsely granular oxyphils	Lymphocytes	Hyaline
77.2 ..	.. 1.1 ..	.. 12.8 ..	.. 7.7

is nearly identical with that of Tables III. and V.¹

Confining our attention for the present to the examination of the white cells, we will leave the other features of these tables for future discussion and consider the

¹ This patient was the subject of somewhat advanced general paralysis, bedridden, quite demented, with no control over his sphincters, a fairly typical case in the third stage of the disease; he had no phthisis or pneumonia, but is the subject of a marked anæmia, occasionally with rise of temperature. The red cells in his blood show an average of 3,250,000 per cubic mm., during a period of fourteen days, and the percentage of hæmoglobin averages 36.6 per cent. The specific gravity is consequently very low, ranging from 1040 to 1043; the white cells are above normal on the whole, and they show a marked increase (represented on the accompanying chart (Chart I.) as a (fine) curve corresponding very fairly with the curve of temperature—notably if the evening temperature alone is considered—though following it at an interval of about twenty-four hours, which conforms with the observations noted by Lewis Bruce.—(*British Medical Journal*, 1901, p. 1600.)

DIFFERENTIAL COUNTS OF THE WHITE CELLS.

(b) *At different periods of the day.*—Under this section two examinations were made daily of three typical cases in the second stage (Tables XII., XIII., XIV.) and four cases in the third stage (Tables VIII., IX., X., XI.)¹

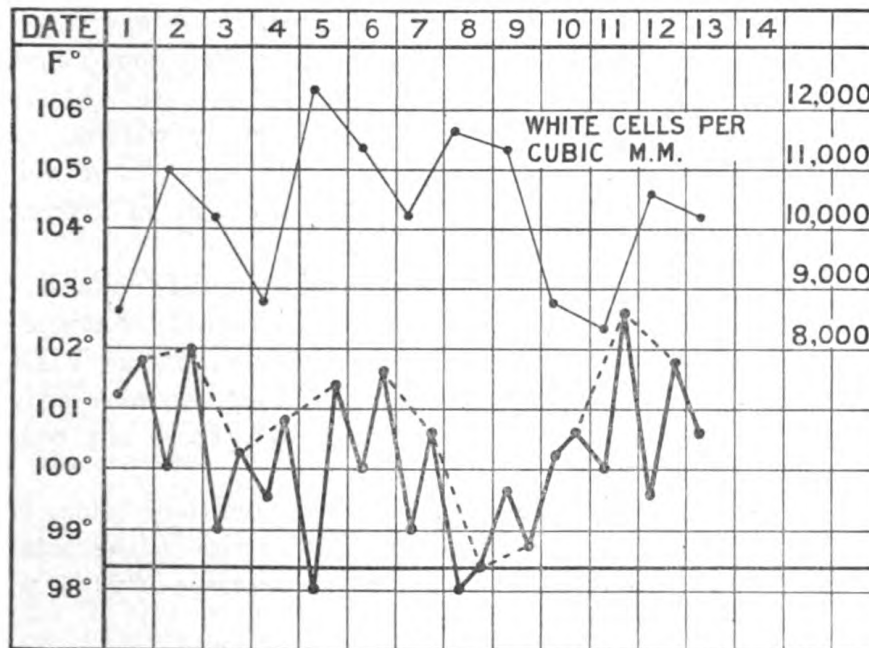


CHART I.

The morning count was taken between 7 a.m. and 8.30 a.m., before the patients had taken food; the evening count, between 5.30 p.m. and 7 p.m., before their evening meal and five and a half to seven hours after their midday meal.

Examinations in Tables I. to VII. were made between 7 a.m. and 8.30 a.m. also, before the patients had taken food. We may compare the mean differential counts obtained from them in the two stages respectively, therefore, with those obtained from the morning count, only in Tables VIII. to XIV., also in the two stages, as they were made under similar conditions.

¹ Tables VIII. and XI. are taken from examination of the same patients from whom Tables III. and V. were drawn up respectively.

Tables	Finely granular oxyphils			Coarsely granular oxyphils			Lymphocytes			Hyaline	
Third stage—											
VIII.-XI.	..	75.5	..	..	.8	..	..	17.2	..	..	6.7
Second stage—											
XII.-XIV.	..	64.4	..	..	3.2	..	..	23.2	..	..	8.9

Here again, therefore, we note that the contrast between the differential count of white cells in the two stages of the disease under examination is well marked.

The subjects chosen for examination in the second stage, Tables XII., XIII., XIV., were three patients still able to get about, and who spent most of their day walking in the airing court. Physically, they were strong and well nourished, and as yet capable, to a great extent, of looking after their immediate needs.

The cases in the third stage were all extremely demented and paralysed, wet and dirty, and quite incapable of attending to any of their wants; while two of them (Tables VIII. and IX.) were greatly emaciated, the other two were only beginning to lose flesh. In no cases were there any bed-sores, cystitis, &c.

The most noticeable result obtained from these tables is that in both stages there is an evening rise in the total number of white cells amounting to an increase of 2,000 to 3,000 cells per cubic millimetre.

In the third stage this leucocytosis is accompanied by a considerable fall in the percentage of finely granular oxyphils and a corresponding rise in the lymphocytes, the hyaline showing practically no alteration.

In the second stage, however, results of the differential counts are not consistent. In one case (XII.) the percentage of finely granular oxyphils is increased; in the second (XIII.) decreased;¹ and in the third their number was unchanged.

It is difficult to determine in how far the increase of white cells is due to digestion.

In three of the above cases (viz., those from which Tables VIII., XIII. and XIV. were obtained) we counted

¹ On account of an error of staining, the slides prepared on six of the thirteen days could not be counted.

the white cells immediately before the first morning meal and at hourly intervals afterwards, with the following results:—

		Number of white cells per c.mm.					
		VIII.		XIII.		XIV.	
Before meal		9,600		6,200		7,600	
One hour later		9,000		7,900		8,400	
Two hours later		10,600		9,400		8,400	
Three hours later		9,900		9,000		7,800	
Four hours later		9,400		6,800		8,000	
Five hours later		10,500		7,000		7,800	

Although there is a slight increase during the second and third hour in these cases, they are not sufficiently consistent for us to draw any very definite conclusions. With regard to the changes in the percentages of the cells in digestion leucocytosis, De Costa,¹ however, states that the gain is usually due "to a predominance of the polynuclear neutrophil forms, with a consequent relative diminution in large and small lymphocytes, but in some instances the differential count remains normal, all forms of cells sharing equally in the increase."

Ewing² regards this as a "mixed leucocytosis, both lymphocytes and polynuclear cells being increased, more especially the lymphocytes."

If this be so the results obtained in Tables VIII., IX., X. and XI., therefore, differ from this account of digestion leucocytosis, in that the polymorpho-nuclear cells are in every case diminished, the lymphocytes, however, being increased.

This is true also of one second stage case, Table XIII., while the reverse condition is found in Table XII.

The leucocytosis noted, moreover, in the tables is present at a much longer interval after the meal (five and a half to seven hours) than that shown on the above table.

DIFFERENTIAL COUNT OF WHITE CELLS.

(c) *During and after convulsion seizures and epileptiform attacks.*—As a result of a series of convulsive seizures in the

¹ "Clinical Hæmatology," 1902, p. 179.

² "Clinical Pathology of the Blood," 1901, p. 124.

second stage of general paralysis a very remarkable change takes place both in the total number of white cells in the blood and in the relative proportion of the different varieties.

The following case illustrates this (Table XV.) :—

J. S., aged 34. On admission, a strong, fair-haired individual, appears dull and stupid, shows signs of mental confusion. Is unconcerned about his position. Pupils unequal, the left with uneven margin. Consensual reaction sluggish. Knee-jerks increased, no ankle clonus obtained. Speech not markedly affected but fails at test words. Later became grandiose, "wonderful in managing horses," constantly boasting of his powers of riding and driving; has earned great sums of money.

Condition of his blood, September 6, 1901, at 7.30 a.m. : 8,200 white cells per cubic mm., 63.8 per cent. finely granular oxyphils, 2.1 per cent. coarsely granular oxyphils, 22.2 per cent. lymphocytes, 11.5 per cent. hyaline, 0.2 per cent. mast cells.

On September 19, between 1.30 p.m. and 3 p.m. he had ten severe convulsions. The bowels were opened by an enema, and thirty grains of chloral given by the rectum. (This, however, was rejected.) Between 5 p.m. and 6 p.m. he had five seizures, and between 7.30 and 8 p.m. three more. Thirty grains of chloral were administered per rectum at 6 p.m. and retained.

The first examination of the blood was made at 3.30 p.m. It was noticed that the blood at this hour was very dark, almost venous in colour, and thick and viscid, so that it flowed very sluggishly.

The number of white cells per cubic mm. was 18,600, of which 93.2 per cent. were of the finely granular oxyphil variety. Half an hour later the number had risen to 23,200, at 4.30 p.m. to 26,200, and at 7 p.m. to 30,800 per cubic mm., the high percentage of the finely granular oxyphils being in each case above 90 per cent.

At 10.30 p.m., at which time the blood still appeared viscid, the white cell count had reached the remarkable number of 43,800 per cubic mm. Up to this time the temperature, as taken in axilla, had not risen.

The following morning, at 7.30 a.m., the temperature in the axilla being 101°, the white cells remained above 27,000. There was a slight fall at 1.30 p.m., with a rise again at 4.30 p.m., the percentage of finely granular oxyphil cells being throughout above 91 per cent.

Of other cells, the hyalines show greatly in excess of the lymphocytes, the coarsely granular oxyphils had practically disappeared, only on one occasion were any of these cells seen, though over 1,000 white cells were counted at each observation.

On the other hand, large typical myelocytes were found in the blood at every observation.

It is worthy of note that while the actual number of lymphocytes and hyaline cells in the blood of this patient, under what may be considered his normal condition, are respectively 2,133 (25·7 per cent. of 9,000) and 684 (7·6 per cent. of 9,000), during the first eight observations, that is, from 3.30 p.m. on the day of the seizures to 4.30 p.m. the following day, the lymphocytes are actually reduced in total number, while the hyalines are much increased. The following table shows the actual numbers :—

			Total number of white cells		Lymphocytes		Hyalines
Sept. 19.	3.30 p.m.	..	18,600	..	130	..	1,134
„ „	4 „	..	23,200	..	556	..	1,020
„ „	4.30 „	..	26,200	..	995	..	1,310
„ „	7 „	..	30,800	..	1,139	..	1,139
„ „	10.30 „	..	43,800	..	1,280	..	1,839
„ 20.	7.30 a.m.	..	27,600	..	1,214	..	993
„ „	1.30 „	..	16,400	..	984	..	492
„ „	4.30 „	..	20,400	..	979	..	816
	Normal	..	9,000	..	2,133	..	684

During the week following this last observation the patient was wildly maniacal, and examination was impossible.

On September 28, however, during the subsequent seven days, observations were taken, and, as Table XV. shows, while the white cell count remains high at first, it shows a tendency to fall from day to day, to October 3, though there is a sudden increase on October 4. At the same time, while the finely granular oxyphils are considerably above the number which we must consider as the normal condition in this patient, in this (the second) stage of the disease the coarsely granular oxyphils are beginning to reappear, and the hyalines are present in a very much larger relative number than the lymphocytes. Myelocytes are still frequently observed in the blood.

We would here draw attention to the remarkable similarity of the blood in this patient—at this date, viz., September 26 to October 4, Table XV.—to that of a patient

in the third stage, for instance, Table IV., the average count during these seven days in the case under notice being :—

Finely granular oxyphils		Coarsely granular oxyphils		Lymphocytes		Hyalines	
79.2	..	..	1.5	..	11.5	..	7.8

which resembles closely the average third stage counts given on page 147.

Other cases of convulsions are given, in Tables XVI., XVII., and XVII*a.* and *b.*

In the case of J. H. (Table XVI.), the convulsions were more uniformly spread over a space of seven and a half hours, and while the rise in the total number of white cells appears to be sudden, the rise of the finely granular oxyphils is more gradual.

The gradual fall in the percentage of the coarsely granular cells is very marked.

The lymphocytes are again very much reduced, giving a percentage very little higher than that of the hyaline cells. Myelocytes are found in several observations.

In the case from which Table XVII. was drawn up, the patient had seven strong seizures in one evening, between 7.30 and 8.30 p.m. An examination of the blood was not made until 2.30 a.m. the following morning, when the number of white cells was 38,000 per cubic mm. with 92.2 per cent. of finely granular oxyphils, the lymphocytes reduced to practically the same number as the hyaline cells, 3 per cent. to 4 per cent. A few myelocytes were seen, and the coarsely granular oxyphils had disappeared.

It was noticed at 2.30 a.m. that the blood was very dark and viscid.

Further observations at 3.30 a.m., 7.30 a.m. and 12.30 p.m., show that this condition was practically maintained until his death at 3.40 p.m.

In the two cases given in Tables XVII. *a* and *b*, the same results are obtained. The "normal" counts are those typical of patients in the second stage of the disease. During the convulsions there is an increased number of total white cells, with an increase in number of the finely

granular oxyphils to 90 per cent., a disappearance of coarsely granular oxyphils, and a reduction in percentage of lymphocytes to that of the hyaline cells.

A few myelocytes were observed.

On comparing the condition of the blood in the above cases of convulsions in general paralysis with that found in a case of *status epilepticus*, certain distinct differences are to be noted.

The case chosen for examination was an epileptic dement, aged 30, whose father, also an epileptic, had died in Wakefield Asylum. This patient had an average of six to ten fits during the week, but was known to develop at intervals of several months the condition known as the *status epilepticus*.

A differential count of his blood some days before the present attack gave the following results :—

White cells per c.mm.		Finely granular oxyphils		Coarsely granular oxyphils		Lymphocytes		Hyaline		Basophils
7,410	..	65.8	..	6.8	..	16.5	..	10.6	..	.2

Table XVIII. gives the results obtained from examination of this case during the condition of status, in which he had thirty-two severe fits during one and three-quarter hours.

It will be seen that there is a considerable rise in the total number of white cells per cubic mm., as in the conditions of general paralysis, described above, but that while the fits are taking place, this is due to a great increase in the number of lymphocytes, which on the first observation are seen to equal in number the finely granular oxyphil cells (41 per cent.). The next two observations taken at intervals of half an hour during the continuance of the fits still show a high percentage of lymphocytes, while the finely granular oxyphil cells, though becoming slightly more numerous, are still fewer in number than in the "normal" count. Myelocytes are present in appreciable numbers in each observation.

Within half an hour of the cessation of the fits (11.15 a.m. to 11.45 a.m.) a marked change has occurred, for the

count now shows a very sudden increase in the percentage of finely granular oxyphil cells, from 56.2 per cent. to 83.7 per cent., with an equally marked decrease in that of the lymphocytes, 29 per cent. to 8.5 per cent.

The coarsely granular oxyphils, which have been numerous in the blood in this case, up to this point, join in this sudden change and become very much reduced in number. It is remarkable that this alteration in character of the differential count, noted between 11.15 a.m. and 11.45 a.m., is not accompanied by any change in the total number of white cells.¹

The actual numbers of lymphocytes and hyaline cells present in the blood in the normal count in this patient are respectively 1,222 and 783; during the first three observations of Table XVIII., from 10.15 a.m. to 11.15 a.m., during the continuation of the fits, both varieties of these cells show an enormous increase; but immediately on the cessation of the fits there is a very sudden decrease in actual number. This is indicated in the following table:—

		Total number of white cells	Lymphocytes	Hyalines
Normal count		7,410	1,222	783
Oct. 8.—	10.15 a.m.	18,700	7,685	2,094
During the status	10.45 „	21,200	5,978	3,816
	11.15 „	21,600	6,264	2,160
After the status	11.45 „	21,800	1,853	1,417
	12.15 p.m.	27,800	1,668	1,807
	1.15 „	28,400	2,669	1,420
"Normal"		7,415	1,223	784

Subsequent examinations show that at the end of two days from the time of onset of the attack, the differential count of the blood had practically returned to the condition which we may look on as normal in this case, although the total number of cells present is above the normal.

Thus the altered conditions found in the blood of the

¹ The enumerations of the white cells in this table were carried out with great care, two distinct observations being made in each case, with a second pipette and counting chamber. As the second result obtained in every case closely agreed with the first, the latter was recorded as being correct.

epileptic during the status epilepticus, when compared to those found in the convulsive seizures of general paralysis (*e.g.* Table XV.) are of a transient nature.

We will now refer to the other data obtained in this research. And as it will be more convenient to note the results obtained under the headings of Specific Gravity, Percentage of Hæmoglobin and Enumeration of Red Cells, as a group, we will consider first:—

The blood pressure.—The examinations under this section are not very complete, the instrument used being somewhat unsatisfactory in determining accurately the blood pressure in the subjects under notice.¹ Such results as were obtained, however, confirm Dr. M. Craig's conclusions,² "that the blood pressure in general paralysis is raised when there is depression, whereas in excited types of the disease, the blood pressure is low, as it is also in the later stages of all types."

The contrast between the mental condition of the cases examined in Tables VI. and XIV. (morning observation only), for instance, was very marked; for while the former was an excitable, restless, and talkative individual, the latter in the morning was dull, morose and lethargic, and this difference is expressed in the contrast between the blood pressure in each case, the average blood pressure in the former being 111.5 m., in the latter 153 m. The average blood pressure in one case in the later stage of the disease, Table III., is also low compared with those of the second stage case, Table XII., XIII., XIV., 119 m. as compared to 136 m., 135 m., 153 m.

The most noticeable result, however, recorded under this section, is the fall in the blood pressure found to occur in the evening in the patients in the second stage of general paralysis, which coincides with a marked change in the mental condition.

¹ We have since used a Gaertner's tonimeter with much more reliable conclusions, but we were unable to obtain this instrument at the time of the present research.

² *Lancet*, "Blood Pressure in the Insane," 1898, p. 1742.

The three cases (Tables XII., XIII., XIV.), at the morning (7 a.m. to 8.30 a.m.) examinations, were dull, depressed and silent, often resenting examination, while in the evening (5 to 7 p.m.) they were cheerful, garrulous and amenable.

This mental change is in each case expressed by a marked difference (*i.e.*, a fall) in the blood pressure.

	Tables	..	XII.		XIII.		XIV.
Morning	..	136	..	135	..	153	
Evening	..	127	..	123	..	135	

(2) *Specific gravity of the blood; percentage of hæmoglobin; enumeration of the red cells; red cell index.*

As it is generally held that there is an intimate relation between the specific gravity of the blood and the number of red cells in it, as expressed by the amount of hæmoglobin, these data determined in the present research will be considered together.

To quote Cabot¹: "The importance of the specific gravity of the blood . . . is not so much of itself, but because it runs parallel to the percentage of hæmoglobin and gives a figure from which the latter can be computed.

"The specific gravity of the blood plasma varies very little (except in dropsy from any cause) and in the corpuscles themselves, the variable element is the hæmoglobin; consequently in most non-dropsical patients the specific gravity of the whole blood varies as directly as the hæmoglobin."

On consulting those tables (III., VI., VII., XII., XIII., XIV.) in which the data under this section are recorded, certain general characteristics are to be noted:—

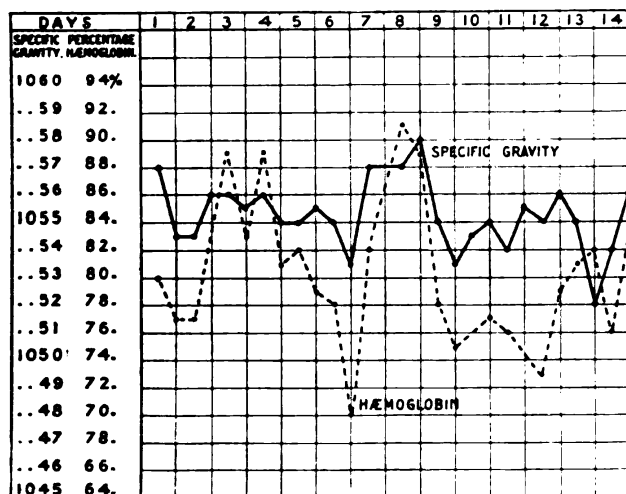
(1) The specific gravity is on the whole lower than normal, as shown by the average (1,048 [XIII.] to 1,057 [VI.]).

(2) The percentage of hæmoglobin is also reduced in every case.

The results agree, therefore, with the observations of Macphail, Lewis and Capps (*vide supra*, p. 143).

¹ Cabot, "Clinical Examination of the Blood," 1897, p. 30.

(3) The number of red cells per cubic mm. is in all cases above normal, averaging well over 5,000,000. They are highest in Table VI., a patient in the early second stage, averaging 5,558,500, but even in Table IV., a patient in the late third stage, the average is 5,307,000. In the two cases in which red cells were enumerated during seizures the same high count is obtained, the average in Table XV. being 5,582,750, with a maximum count of 5,940,000, the single observation in Table XVII. giving a result of 5,320,000.¹



FROM TABLE XII.

(4) In consequence of the increased number of red cells and reduced percentage of hæmoglobin, the red cell index (calculated from a hæmoglobin percentage of 100 in 5,000,000 corpuscles) is much below unity.

That the relation existing between the specific gravity and hæmoglobin in the blood is on the whole maintained, is shown by the following charts, where these data are graphically represented as curves (from Tables III., XII., XIII., XIV.), in which the hæmoglobin and specific gravity curves on the whole correspond fairly closely.

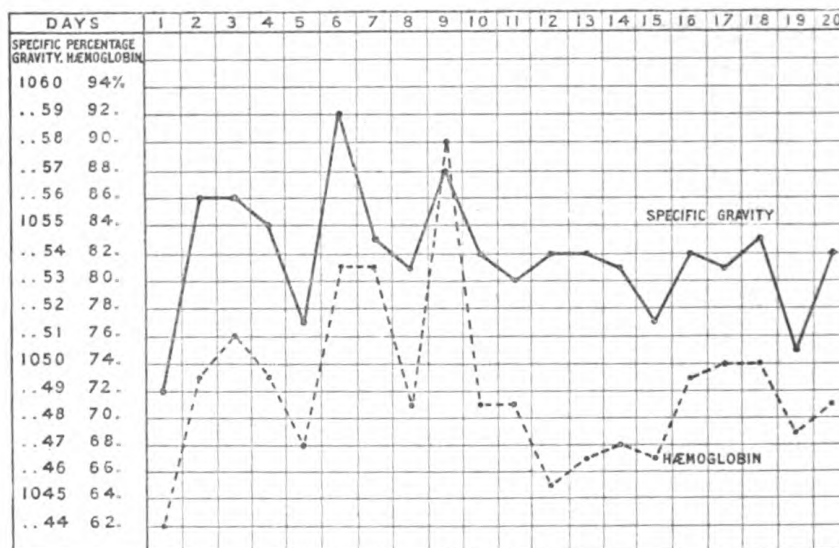
¹ The results are directly opposed to those recorded by previous observers, but we submit them with confidence, for second and third enumerations were constantly made to check the results first obtained.

SUMMARY OF RESULTS.

In the blood of patients suffering from general paralysis :—

(1) In the second stage of this disease the finely granular oxyphil cells are reduced below the percentage normal in health. The mono-nuclear cells are increased.

(2) In the third stage of the disease the finely granular oxyphil cells are increased to a percentage much above that normal in health. The mono-nuclear cells are much diminished.



FROM TABLE III.

(3) In both stages, of mono-nuclear cells the large hyaline forms are relatively more abundant than the lymphocytes.

(4) The coarsely granular oxyphil cells, *i.e.*, eosinophils, are as a rule numerous in the second stage, scanty in the third.

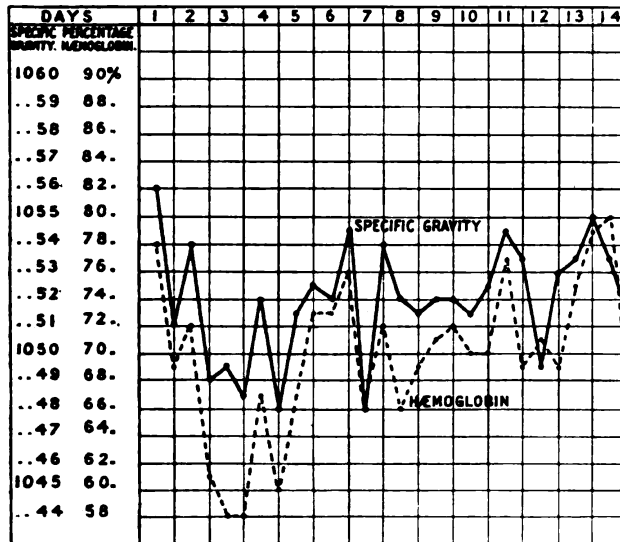
(5) Mast cells are occasionally found and are most numerous when eosinophils are abundant.

(6) Myelocytes are occasionally found.

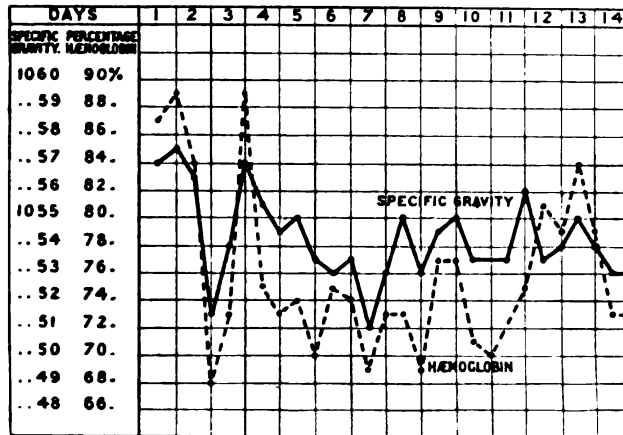
(7) There is an evening rise in the total number of white cells in all cases, amounting to from 2,000 to 3,000 per cubic mm., which in the third stage, at any rate, is marked

by a diminution in finely granular oxyphils and increase of lymphocytes.

(7a) There appears to be no marked increase of leucocytes due to digestion in those few cases examined, and such as there is the increase is not characteristic.



FROM TABLE XIII.



FROM TABLE XIV.

In convulsive seizures of general paralysis:—

(8) There is a very marked and sudden increase in the total number of white cells in the blood resulting from a

series of convulsions, so that they may in a few hours be multiplied four- or sixfold.

(9) This increase appears apparently immediately after the onset of the attacks.

(10) This increase consists of finely granular oxyphil cells, which form 90 per cent. and over of the total differential count.

(11) The lymphocytes are greatly reduced in percentage and very much reduced in actual number per cubic mm.

(12) While the percentage of hyalines is only slightly reduced, the actual number of these cells per cubic mm. is increased.

(13) The coarsely granular oxyphil cells almost entirely disappear.

(14) Myelocytes appear in the blood in appreciable numbers.

(15) These changes are maintained for a considerable period of time (two or three weeks in one case), the return to normal¹ condition taking place gradually.

(16) The differential count found in convulsions passes before returning to the normal condition, through a stage closely resembling that found in the third stage.

(17) The extent of leucocytosis appears to be proportionate to the severity and number of the convulsions.

(18) The blood in the third stage of the disease and during convulsions appears dark in colour, viscid, and flows with difficulty.

(19) In the status epilepticus there is also a great and sudden increase in total number of white cells, but during the fits :—

(a) The finely granular oxyphils are diminished, the lymphocytes greatly increased.

(b) On cessation of the fits, the finely granular oxyphils show a very sudden increase in number, the lymphocytes being equally rapidly reduced.

(c) The coarsely granular oxyphils, unchanged during the status, rapidly disappear on cessation of the fits.

¹ *I.e.*, normal to the patient.

(d) Myelocytes are numerous during the status.

These changes appear to be transient, the normal condition of the blood being restored in two or three days.

(20) The blood pressure in general paralysis is low in conditions of mental excitement and during the late stages of the disease and high in conditions of mental depression.

(21) It is higher in the morning than in the evening, this corresponding with a change in the mental condition from depression to exaltation.

(22) The specific gravity of the blood is lower than in health.

(23) The percentage of hæmoglobin is considerably reduced, especially in the later stages.

(24) The number of red cells is higher than that found in normal blood.

(25) The red cell index is reduced.

(26) The normal relation between specific gravity and amount of hæmoglobin in the blood is on the whole well maintained.

TABLE I.
DIFFERENTIAL COUNTS IN THIRD STAGE OF GENERAL PARALYSIS.

Case	Stage	Finely granular oxyphil	Coarsely granular oxyphil	Lymphocytes	Hyaline	Coarsely granular basophil	Various
1	Third	80	·2	4·3	15·4	..	·1
2	"	81·9	2·2	5·5	9·5	·1	·2
3	"	85	·6	6	7	·2	
4	"	83	1·6	6·5	8	..	·1
5	"	77·9	2·2	8·7	9·9	..	·4
6	"	80	·8	13·2	6		
7	"	81·4	·4	11·1	5·3	..	·2
8	"	78·6	1·2	12·2	8		
9	"	81	·7	12	6·8		

TABLE II.
DIFFERENTIAL COUNTS IN EARLY SECOND STAGE.

Case	Finely granular oxyphil	Coarsely granular oxyphil	Lymphocytes	Hyaline	Various	Mental state
1	63·2	·4	22·5	13·9	·7	Fair.
2	37·5	7	30	25·3	·2	Demented.
3	59·6	1·5	25·3	13·6	..	"
4	61·4	2	23·2	13·2	·2	Fair.
5	63·3	2	21·5	13·2	..	Good.
6	60·5	2·2	25·8	11·2	·3	"
7	60	6·2	20	13·8	..	"
8	60	1·2	27·1	11·7	..	Demented.
9	52	1·5	30	16·3	·2	Emotional.
10	56·8	2	31	10	..	Fair.
11	57·8	4·1	27·1	11	..	Good.
	63·8	2·1	22·4	11·5	..	Fair.
TWO CASES IN LATE SECOND STAGE.						
11	72	·7	15·7	11·4	·1	Very demented.
12	72·3	1	17·6	8·4	·7	" "

TABLE III.

DAILY EXAMINATION OF A THIRD STAGE CASE. DIFFERENTIAL COUNT.

Day	Temper- ture	Blood pressure	Specific gravity	Hemo- globin per cent.	Red cell index	Red cells per c.mm.	White cells per c.mm.	Number of red cells to one white	Finely granular oxyphl	Coarsely granular oxyphl	Lympho- cytes	Hyaline	Various
	Degrees												
1	98.2	112	1050	63	.48	5,436,000	8,600	632	82	.9	9.4	7.7	.5
2	97.8	120	1056	73	.65	5,608,000	9,800	571	74.7	.6	16.1	7.8	.2
3	98.2	115	1056	76	.74	5,109,500	7,400	690	82.6	.5	9.3	6.6	1
4	97.4	115	1055	73	.73	4,952,000	11,200	440	82.9	.3	9.3	7	.3
5	98.4	125	1051.5	63	.63	5,316,000	8,600	618	84	.6	11	3.7	.3
6	98	127	1059	82	.69	5,860,000	11,200	523	84.8	.7	10.5	3	.8
7	97.8	125	1054.5	82	.69	5,868,000	10,000	586	81	1.1	13	3.8	.8
8	98.2	115	1053.5	71	.62	5,712,000	7,270	785	83	.5	13.3	2.3	
9	98	125	1057	91	.84	5,376,000	7,700	695	81	.5	15.3	2.7	.3
10	98.6	117	1054	71	.65	5,408,000	8,600	629	86.7	1.1	9.6	3.2	.5
11	98.4	120	1053	71	.62	5,720,000	9,400	608	84.9	.5	11.5	3	.2
12	97.6	120	1054	65	.60	5,368,000	8,800	610	80	1.3	11.6	7	
13	98.2	122	1054	67	.70	4,748,000	8,200	578	80	1.4	11.2	7	.4
14	97.8	116	1053.5	63	.61	5,536,000	7,400	748	77.8	1.7	11.2	8	1
15	99	115	1051.5	67	.64	5,204,000	7,700	675	80.9	1.7	11	6.3	
16	97.8	120	1054	72	.77	4,624,000	9,500	486	81.5	1	8.4	8.7	.4
17	97.6	123	1053.5	73	.68	5,332,000	9,800	544	80.5	1.2	11.6	7	.5
18	..	..	1054.5	73	.77	4,732,000	8,200	577	77.4	1.1	13.8	7.3	.3
19	97.6	..	1051	69	.61	5,600,000	9,000	622	83.5	1.9	8.9	4.6	1
20	..	..	1054	71	.67	5,244,000	7,400	708	80.5	1.3	10	7.8	.4
Average	..	119	1054	72.2	.66	5,307,000	8,780	..	81.5	.9	11.3	5.7	
											17		

TABLE IV.
CASE IN THIRD STAGE. LEUCOCYTOSIS VARYING WITH THE TEMPERATURE. DIFFERENTIAL COUNT.

Day	Temperature	Specific gravity	Hemo- globin per cent.	Red cell index	Red cells per c. mm.	Number of red cells to one white	White cells per c. cm.	Finely granular oxyphil	Coarsely granular oxyphil	Lympho- cytes	Hyaline	Various
	Degrees											
1	101.2-101.8	1040.5	33	.51	3,202,000	372	8,600	81.2	.1	12	6.3	.4
2	100 — 102	1042	37	.60	3,048,000	277	11,000	86	.3	10	3.7	
3	99 — 100.1	1040	34	.53	3,208,000	314	10,200	70.6	3	12.4	12.6	.4
4	99.6-100.8	1040	34	.47	3,568,000	405	8,800	74.5	1.3	20.6	2.8	.3
5	98 — 101.4	1040.5	37	.61	2,854,000	230	12,400	74.2	2.4	13	10.4	
6	100 — 101.6	1043	37	.55	3,348,800	293	11,400	77	2	14.4	6.6	
7	99 — 100.6	1041	35	.53	3,346,000	318	10,200	77.8	1.3	12.5	6.2	2
8	98 — 98.4	1043	39	.48	4,072,000	351	11,600	80	.6	14	5.2	.1
9	99.6- 98.8	1043	38	.65	2,918,000	343	11,400	77.8	1.5	10.7	9.5	.3
10	100.2-100.6	1040.5	37	.66	2,792,000	313	8,900	73.2	2	13.1	10.2	.2
11	100 — 102.6	1043	39	.62	3,128,000	332	8,400	78	1.7	12.7	7.4	
12	99.6-101.8	1043	39	.58	3,332,000	314	10,600	82	.7	8.7	5.5	2.9
13	100.6-100	1040.5	37	.52	3,536,000	340	10,400	72	1.3	12.7	13.6	.8
Average		1041	36.6	.56	3,250,000	..	..	77.2	1.1	12.8	7.7	
										20.5		

TABLE V.
THE SAME CASE IN THIRD STAGE. TEMPERATURE WITHIN NORMAL LIMITS. DIFFERENTIAL COUNT.

Day	Temperature Degrees	Specific gravity	Hemo- globin per cent.	Red cell index	Red cells per c.mm.	Number of red cells to one white	White cells per c.mm.	Finely granular oxyphil	Coarsely granular oxyphil	Lympho- cytes	Hyaline	Various
1	97.4	1040	33	.44	3,694,000	473	7,800					
2	97.4-99	1041	43	.62	3,440,000	441	7,800	66.8	.3	24.5	8.4	
3	97.2-99	1040	33	.55	2,966,000	593	5,000	74.4	.7	18.6	6	.2
4	97.4-97.8	1038	37	.64	2,880,000	436	6,600	74.5	1.1	21.1	5.5	F .3
5	97 -97.8	1038	35	.67	2,780,000	328	8,300	70	4.8	18.8	6.2	
6	98 -98.6	1040	39	.58	3,314,000	615	5,400	76.3	.7	13.4	9.6	
7	98.6-97.8	1039	36	.59	3,084,000	514	6,000					
8	97.8-99	1040	37	.54	3,408,000	501	6,800	81.7	.5	12.3	5.4	
9	97.6-98.4	1040	36	.45	3,920,000	512	6,400	64.7	.7	26.5	8.1	
10	97.8-98.4	1041	37	.52	3,484,000	483	7,200	75.6	.6	15.8	8.9	
11	98 -98.6	1041	43	.67	3,200,000	250	12,800	78.2	.5	13.7	7.6	
12	97.2-98.6	1040	39	.51	3,392,000	458	7,400	80	1.3	12.7	6	
13	98 -98.8	1041	42	.62	3,364,000	485	7,000	76.3	.0	15.4	7.6	
14	97.4-98.6	1041	38	.52	3,612,000	564	6,400	79.8	.2	14.3	3.6	
Average ..	..	1040	37.7	.56	3,327,700	..	7,193	74.8	1	17.3	6.7	24

TABLE VI.
DAILY EXAMINATION IN SECOND STAGE (EARLY). DIFFERENTIAL COUNT.

Day	Tempera- ture	Blood pressure	Specific gravity	Red cells per c.mm.	Hæmo- globin per cent.	Number of red cells to one white	Red cell index	White cells per c.mm.	Finely granular oxyphil	Coarsely granular oxyphil	Lympho- cytes	Hyaline	Baso- phil	Others
1	Degrees 98.2	125	1059	4,708,000	81	574	.86	8,200	63.8	2.2	29.5	4.2		.1
2	98	125	1056	5,910,000	73	568	.62	10,400	57.3	5.2	25	8.1	.4	
3	99	115	1055.5	5,264,000	81	674	.75	7,800	65.7	3.5	22	8	.4	.4 m.
4	98	115	1060	5,588,000	91	582	.81	9,600	65.7	3.7	19.1	12.5		
5	98.4	110	1056.5	5,604,000	83	824	.72	6,800	65.2	3.2	23	8.5		
6	98.2	120	1058	5,400,000	93	435	.84	12,400	66.1	4.2	18.5	1.02	.5	.1 m.
7	98	97	1057	5,828,000	89	633	.75	9,200	63.6	4	23.2	9		.3 m.
8	98	106	1059	5,712,000	93	772	.81	7,400	69.3	3.8	17.8	9.1		
9	96.8	107	1057.5	5,536,000	87	582	.78	9,500	62	4.3	17.2	16.5		
10	96.8	105	1057	5,700,000	87	730	.76	7,800	62.9	4.4	18.7	13		
11	97.6	109	1057.5	5,500,000	93	743	.84	7,400	62.7	5.2	23	9		
12	97.2	110	1057.5	5,728,000	87	716	.75	8,000	61.7	5	22.7	10.2	.3	.1
13	97.8	106	1056	5,784,000	84	875	.72	6,600	63.4	4.9	20.1	10.8	.5	.2
Average	..	111.6	1057.5	5,558,500	86.3	..	.77	8,540	63.8	4.1	21.5	10		
												81.5		

TABLE VII.
DAILY EXAMINATION IN A SECOND STAGE CASE. DIFFERENTIAL COUNT.

Day	Temperature	Specific gravity	Hemo- globin per cent.	Red cells per c.mm.	Number of red cells to one white	Red cell index	White cells per c.mm.	Finely granular oxyphil	Coarsely granular oxyphil	Lympho- cytes	Hyaline	Various
1	Degrees 98.2	1054	77	5,664,000	858	.68	6,600	62.8	.4	26.2	10.2	.4
2	98.6	1055	76	5,440,000	604	.69	9,000	64.2	2	20.6	12.8	.3
3	99	1053	82	5,360,000	394	.76	13,600	65.6	1.5	22.8	10	.1
4	97.4	1053	77	5,312,000	566	.72	9,200	69.8	.3	22.2	7.7	
5	97.4	1053	73	5,412,000	614	.67	6,800	66.8	.5	25.7	7	
6	97.6	1053	73	5,192,000	625	.70	8,300	67.2	1.4	22.7	8	.7
7	98.4	1053	79	4,896,000	510	.78	9,600	71.7	.7	20.5	7	
8	98	1054	77	4,488,000	521	.85	8,600	60	1.3	27	10.6	1.1
9	98	1054	79	5,064,000	538	.78	9,400	61.7	.9	28.5	8.6	.3
10	89.4	1054	75	5,368,000	536	.70	10,000	61.7	1.2	25.2	11.1	.8
11	..	1054	69	5,680,000	747	.60	7,600	65.5	.7	25.2	8	
Average	..	1053.5	76.2	5,261,454	..	.72	9,725	65.2	.9	24.3	9.3	
											33.6	

TABLE VIII.

THIRD STAGE.

Counts taken : Morning, 7 to 8 a.m., before meals ; evening, 5 to 6 p.m., before meals.

Day	Temperature	White cells per c.mm.	Finely granular oxyphil	Coarsely granular oxyphil	Lympho- cytes	Hyaline
1	Degrees					
	M., 97	11,400	80	.8	15.8	3.6
2	E., 98	12,100	77.2	.2	20	2.6
	M., 97.8	9,200	78.7	.4	14.1	6.8
3	E., 97.8	12,150				
	M., 97.6	7,100	85.5	.5	11.1	2.9
4	E., 98.2	11,200	74.6	.3	20	5.1
	M., 97.4	11,500	84	.4	10.5	5.1
5	E., 98	13,000	79	..	17.5	3.5
	M., 97.2	10,800	76	.4	14.3	9.3
6	E., 98	10,200	72.7	.7	16.7	9.9
	M., 97	12,500	81.9	.8	12.3	4.9
7	E., 97.8	12,800	70.4	1.3	21.8	6.4
	M., 97.2	9,800	79.4	.4	15	5.2
8	E., 98.2	11,600	70	1.1	17.5	11.4
	M., 97	10,800	79.1	2.4	11.4	7.1
9	E., 97.6	14,600	74.3	1.5	16	8.1
	M., 97.2	10,000	77.7	.7	15.8	5.7
10	E., 97.8	11,200	76	1.1	16	6.8
	M., 97.6	8,800	81	.8	11.7	6.4
11	E., 98.4	10,800	70.8	.7	16.3	5.1
	M., 101	13,800	90.6	.1	5.4	3.8
12	E., 98	22,000	76.9	1.6	14.8	6.5
	M., 97.2	9,880				
Average	E., 98	15,400				
	M., 98.4	10,400	81.2	.7	12.4	5.5
	E., 98	12,985	74.8	.9	17.6	6.5

TABLE IX.

THIRD STAGE.

Counts taken: Morning, 7 to 8 a.m., before meals; evening, 5 to 6 p.m., before meals.

Day	Temperature	White cells per c.mm.	Finely granular oxyphil	Coarsely granular oxyphil	Lympho- cytes	Hyaline	Others
1	Degrees. M., 97	8,900	69	·5	22·4	8·1	
	E., 98·8	10,200	58·2	·6	32·4	8·7	·1
2	M., 97·4	7,600	69·1	·5	22·5	7·9	
	E., 98·2	7,200	63·8	·9	30·7	4	·5
3	M., 97	8,100	66·4	·3	24·3	8·6	·3
	E., 97·6	9,200	59·6	·7	30·7	8·5	·3
4	M., 97·2	7,500	70·6	·4	23·5	5·4	
	E., 98	8,200	62·8	·1	29·5	6·7	
5	M., 97	10,400	70·6	·7	16·5	11·5	·7
	E., 97·8	10,000	65	2·6	24·8	7	·5
6	M., 99·2	8,800	72·3	·7	21·4	5·6	
	E., 100·2	9,400	62·1	·4	27·7	9·4	·4
7	M., 97	8,600	73·6	..	19·	7·4	
	E., 98	9,200	58·3	..	35·6	5·7	·4
8	M., 96·8	11,200	75·6	·7	18·3	5·2	·2
	E., 97	11,000	55·4	1·3	35·7	7·6	
9	M., 96·4	7,800	68·6	·7	21·9	8·7	
	E., 98	9,200	48·7	·7	40·2	10·4	
10	M., 97·2	11,000	70·6	·5	21·5	7·3	
	E., 97·4	10,200	68·9	·1	24·5	6·4	
11	M., 97	5,800	63·7	·6	29·5	6·2	
	E., 97·4	7,400	54·9	·3	38·3	6·5	
12	M., 97·2	7,600	65·4	·6	27	7	
	E., 98	7,000	59·3	·3	33·8	6·5	
Average	M., 97·2	8,633	69·6	·5	22·3	7·4	
	E., 98	9,015	59·5	·8	32	7·3	

TABLE X.

THIRD STAGE.

Counts taken: Morning, 7 to 8 a.m., before meals; evening, 5 to 6 p.m., before meals.

Day	Temperature	White cells per c.mm.	Finely granular oxyphil	Coarsely granular oxyphil	Lympho- cytes.	Hyaline	Others
1	Degrees M., 98	7,800	81.5	.4	11.1	5.3	.2
	E., 96.6	11,000	70	1.2	23.4	6.4	
2	M., 98	7,000	76.5	.4	15.5	7.6	
	E., 98.6	8,100	60	.9	27.6	11.4	
3	M., 97	7,400	73.3	1.7	17.3	7.7	
	E., 97.8	8,400	59.4	1	29.6	10	
4	M., 97.2	8,000					
	E., 99.2	8,600	63	1.5	28.6	6.8	
5	M., 98	8,400	74.6	.2	19	6.2	
	E., 99	8,600	52.6	2.1	37	7.3	.9
6	M., 98.8	7,500					
	E., 98.4	7,800	63.7	.7	25.2	10.4	
7	M., 98.2	7,000	74.6	2	15.3	7.7	.4
	E., 98	8,200	59.9	1.4	25.7	12.5	.5
8	M., 98	9,400	75	.5	18.7	5.8	
	E., 98.2	8,200	62.2	1.8	30.9	5.1	
9	M., 97.4	7,400	73.4	1.4	18.9	6.3	
	E., 98.2	8,400	59.5	1	30.3	9.1	
10	M., 98	9,600	75	1.5	16.5	7	
	E., 98.6	9,600	67.3	1.5	23.9	7.1	
11	M., 98	7,800	72	1.5	20.2	6.3	
	E., 99.4	8,200	60.6	1.2	32.2	6	
12	M., 97.8	8,200	76.1	.6	18.2	5	
	E., 98.4	10,200	59.4	1	35.2	4.3	
Average	M., 97.7	7,860	75.2	1	17	6.5	
	E., 98.3	8,775	61.3	1.2	30	6	

TABLE XI.

THIRD STAGE.

Counts taken : Morning, 7 to 8 a.m., before meals ; evening, 5 to 6 p.m., before meals.

Day	Temperature	White cells per c.mm.	Finely granular oxyphil	Coarsely granular oxyphil	Lympho- cytes	Hyaline	Others
1	Degrees						
	M., 97.4	7,800	66.8	.3	24.5	8.4	
2	E., 99	8,800	65.8	1.6	20.7	11.6	
	M., 97.2	5,000	74.4	.7	18.6	6.2	
3	E., 99	8,600	68.7	1.7	23.8	5.1	.5
	M., 97.4	6,600	74	1.1	21.1	3.5	.3
4	E., 97.8	7,800	71.1	1.2	22	5.7	
	M., 97.8	8,300	70	4.8	18.8	6.2	
5	E., 97.8	9,200	81.6	2	9.8	6.5	
	M., 98	5,400	76.3	7	13.4	9.5	
6	E., 98.6	8,200	72.1	3	18	6.9	
	M., 96.8	6,000					
7	E., 97.8	8,000	73.8	1.4	18.8	6	
	M., 97.2	6,800	81.7	.5	12.3	5.4	
8	E., 98.6	6,200	66.6	.3	26	7	
	M., 96.8	6,400	64.7	.7	26.5	8.1	
9	E., 97.2	7,400	67.7	1.3	19.3	4.6	
	M., 97	7,200	70.9	1.4	20	7.7	
10	E., 98	7,800	68.1	.6	23.2	7	
	M., 97.2	12,800	71.9	.7	18.2	9	
11	E., 98	9,200	66.4	1	23.5	9	
	M., 97	7,400	70	1.3	16.2	12.5	
12	E., 97.4	8,150					
	M., 97	7,000	74.3	.3	19.2	5.2	
Average	E., 98.6	7,800	62.7	1.6	28	7.7	
	M., 97.4	7,150	75.9	1.1	17.1	7.4	
	E., 97.8	7,950	69.5	1.4	21.2	7.6	

TABLE XII.
COMPLETE EXAMINATION, MORNING AND EVENING, SECOND STAGE.

	Temperature	Blood pressure	Specific gravity	Hemo- globin per cent.	Red cell index	Red cells per c.mm.	White cells per c.mm.	Number of red cells to one white	Finely granular oxyphil	Coarsely granular oxyphil	Lympho- cytes	Hyaline	Others
1	M., 98 E., 98	140 135	1057.5 1054.5	80 77	.69 .83	5,792,000 4,636,000	6,200 9,800	934 466	61 66	6.2 2.1	24 22.2	8.6 9.7	.1
2	M., 97.6 E., 98.4	140 137	1054.5 1056	77 81	.74 .75	5,136,000 5,400,000	6,200 8,600	828 674	64 60.8	3.2 3.6	24.4 24.7	8.2 10.9	
3	M., 98 E., 98.6	145 135	1056 1055.5	89 88	.80 .87	5,512,000 4,740,000	4,600 8,500	1,197 557	55.5 50.6	7.2 2.8	26 29.4	10.7 8.4	.6
4	M., 98.4 E., 98.6	133 120	1056 1055	81 81	.91 .81	5,288,000 4,960,000	5,400 6,500	979 729	61 71.2	3.6 4.2	24.7 30.1	10.5 10.5	.2
5	M., 97.6 E., 99.4	138 125	1055 1055.5	82 79	.. .76	.. 5,152,000	6,800 13,200	.. 390	55.2 68	4.2 1.4	24 24	15.8 14.6	.2
6	M., 97.6 E., 99.2	130 123	1055 1053.5	78 69	.74 .68	5,244,000 5,020,000	6,600 10,200	794 492	57 57	3.3	24	14.6	.2
7	M., 98.8 E., 100.4	137 120	1057 1057	82 85	.77 .79	5,308,000 5,368,000	10,900 12,800	486 491	63 67.3	2 .8	25.4 17.9	9.5 13.9	.1
8	M., 98.4 E., 100.2	127 125	1057 1058	91 89	.89 .78	5,060,000 5,700,000	11,600 10,200	427 558	60.9 72.3	1.7 .9	27.7 16.2	9.7 10.6	
9	M., 98 E., 99.6	132 123	1055 1053.5	78 85	.72 .78	5,356,000 4,756,000	10,200 10,600	525 446	61 65.2	2.5 1.8	21.3 23.2	15.2 9.8	
10	M., 97.4 E., 98	137 128	1054.5 1055	76 77	.70 .70	5,380,000 5,500,000	7,000 8,000	769 687	60 63.3	2.6 1	22 21.7	15.4 13.6	.4
11	M., 97 E., 98		1054 1055.5	76 75	.70 .74	5,396,000 5,080,000	7,800 9,400	694 527	59.7 61.1	4.8 5.3	28.9 20.2	6.4 13.4	.2
12	M., 98 E., 99.2		1055 1056	73 79	.70 .71	5,200,000 5,566,000	8,700 10,200	618 546	61.8 65.5	6.3 5	20.4 18	11.5 11.5	
13	M., 97 E., 98.6		1055 1052	81 82	.83 .71	4,856,000 5,712,000	5,200 8,600	931 664	57.3 65	4.2 3.9	25.2 19.2	13.2 11.5	.1
14	M. E.		1054 1056	76 83	.72 .65	5,230,000 5,549,000	7,600 9,600	688 579	60.2 67.4	5.3 6.1	24.6 18	9.6 8.5	.3
Aver- age	M., 98.6 E., 99.6	136 127	1055.5 1055.2	80	.76	5,254,777	7,450 (9,728		59.8 6.56	4 2.7	24.9 20.2	10.9 11.6	

TABLE XIII.

COMPLETE EXAMINATION, MORNING AND EVENING, SECOND STAGE.

	Temperature	Blood pressure	Specific gravity	Hemo- globin per cent.	Red cell index	Red cells per c. mm.	White cells per c. mm.	Finely granular oxyphil	Coarsely granular oxyphil	Lympho- cytes	Hyaline	Others
1	Degrees M., 97.8	132	1056.5	79	.68	5,763,000	6,600	68.4	4.7	16.5	9.3	.8
2	E., 98.2	120	1051	64	.60	5,908,000	8,400	57.4	4	31.6	7	
3	M., 97	135	1054	72	.83	5,328,000	8,200					
4	E., 98.4	127	1049	61	.54	5,588,000	10,800					
5	M., 97.6	130	1049.5	59	.61	4,820,000	4,000					
6	E., 97.6	125	1048.5	59	.57	5,928,000	10,000	62.9	3.1	22	12	
7	M., 98	135	1052	67	.77	4,440,000	6,200	59.2	1.8	27.8	11.2	
8	E., 98.2	118	1048	60	.56	5,908,000	8,200	68.5	2	24	5.5	
9	M., 97.6	142	1051.5	69	.55		7,000	58.1	1.7	32	8.2	
10	E., 98.6	127	1052.5	73	.72	5,048,000	8,100					
11	M., 98	135	1052	73	.82	4,420,000	6,400					
12	E., 97.6	120	1054.5	76	.74	5,126,000	7,600					
13	M., 97.6	132	1048	66	.67	4,900,000	5,900	64.9	1.3	25.8	8	
14	E., 97.6	119	1054	72	.73	4,880,000	11,800	57	1.3	26	15.7	
15	M., 96.6	133	1052	67	.67	4,964,000	5,800	65.1	4	19	11.9	
16	E., 97.4	122	1051.5	69	.67	5,084,000	8,800	59.2	2.1	27.4	11.3	
17	M., 98	140	1052	71	.81	4,980,500	6,000	68.5	2	20.2	9.2	.1
18	E., 98.4	127	1052	72	.68	5,228,000	11,500	54.2	.9	27.3	17.6	
19	M., 97.8	142	1051.5	70	.64	5,600,000	5,600					
20	E., 97.2	125	1052.5	70	.62	5,636,000	9,000					
21	M., 97.8	..	1054.5	77	.70	5,444,000	6,800	67.3	2.6	21.7	8.4	
22	E., 97.4	..	1053.5	69	.67	5,080,000	9,600	59.2	1	25.2	14.6	
23	M., 97.4	..	1049.5	71	.68	5,568,000	7,400					
24	E., 98	..	1053	72	.69	5,152,000	8,200					
25	M., 98.4	..	1053.5	75	.78	4,792,000	6,000					
26	E., 98	..	1055	79	.73	5,408,000	8,200					
Aver- age	{ M., 98.3 E., 98.6	135 123	1048 1052	70	.68	5,263,000	6,300 9,244	66.5 56.7	2.8 1.7	21.3 28.2	9.2 12.2	

TABLE XIV.
COMPLETE EXAMINATION, MORNING AND EVENING, SECOND STAGE.

	Temperature	Blood pressure	Specific gravity	Hæmoglobin per cent.	Red cell index	Red cells per c.mm.	White cells per c.mm.	Number of red cells to one white	Finely granular oxyphil	Coarsely granular oxyphil	Lymphocytes	Hyaline	Others
	Degrees												
1	M., 98.2	150	1057	87	.74	5,888,000	6,800	864	70.4	2.2	22.3	5.7	.4
	E., 98.8	140	1057.5	89	.89	4,972,000	8,600	462	74.3	4	15.3	7.2	
2	M., 97.8	158	1056	85	.87	4,860,000	8,000	607	70	3	20	6.5	.2
	E., 98.6	140	1051.5	67	.57	5,894,000	10,600	556	62.1	3.3	28.6	5.8	
3	M., 98.2	140	1054.5	74	.67	5,532,000	5,600	980	62.2	3.5	26.3	8	.1
	E., 99	135	1057	89	.92	4,832,000	12,200	396	70.3	2	19	8.7	
4	M., 97.6	145	1055.5	75	.69	5,424,000	7,400	772	67.4	2.7	22.3	7.6	.2
	E., 98	137	1054.5	73	.67	5,428,000	10,200	532	65	3	22.2	9.6	
5	M., 97.4	157	1055	74	..	..	7,500	706	70.3	2.3	18.5	8.3	.3
	E., 98.2	135	1053.5	70	.59	5,928,000	13,600	436	67.3	2.9	23.7	7.2	
6	M., 97.8	153	1053	75	.68	5,512,000	6,800	807	63.2	3.7	27.8	5.3	
	E., 99	135	1053.5	74	.66	5,600,000	11,600	482	64	2.5	23	9.5	.9
7	M., 97	150	1051	69	.72	4,784,000	8,600	556	59	1.7	30	8.8	.5
	E., 98	127	1053	73	.71	4,944,000	11,600	426	60.9	2.6	27.2	9.1	.2
8	M., 97.2	157	1055	73	.78	4,660,000	9,200	506	70	2.8	20	6.9	.3
	E., 99	132	1053	69	.61	5,648,000	11,500	491	68.1	4.4	18.4	9.1	
9	M., 97.4	162	1054.5	77	.72	5,300,000	8,600	616	68.9	3	21.5	6.4	.2
	E., 98	132	1055	77	.75	5,132,000	10,600	485	64	3.7	24.7	7.6	
10	M., 97	157	1053.5	71	.66	5,319,000	8,000	664	69.5	1.7	22.4	6.4	.1
	E., 98.4	137	1053.5	70	.66	5,232,000	10,200	513	65.5	2	22.4	9	
11	M., 97		1053.5	72	.66	5,411,000	8,800	614	64.7	2.8	27.1	5.4	.3
	E., 97.6		1056	75	.68	5,360,000	10,600	505	64.8	3.2	25	6.7	
12	M., 97.4		1053.5	81	.73	5,536,000	9,200	565	67.4	3	25	4.6	
	E., 99.2		1054	79	.77	5,120,000	11,400	446	66	2.3	23.2	8.5	.8
13	M., 97.4		1055	84	.78	5,360,000	6,600	812	67	3.8	22.5	6.3	
	E., 98		1054	79	.71	5,540,000	8,600	644	65.6	3.5	22.5	7.8	.6
Aver- age	M., 98.1 { E., 98.5	153 135	1054 1054	79	.71	5,540,800	7,692 10,870		66.9 66	2.8 3	23.5 22.7	6.6 8.1	

TABLE XV.

CONDITIONS DURING CONVULSIVE SEIZURES.

Sept. 19, 1901 .. 10 seizures between 1.30 and 3 p.m.

" " 5 " " 5 " 6 "

" " 3 " " 7.30 " 8 "

At 3.30 p.m. the blood was dark, thick, appearing viscid, and flowing with difficulty.

" 4.30 " " more fluid and brighter in colour.

" 10.30 " " again thick and viscid.

	Tempera- ture	Specific gravity	Red cells per c.mm.	Hæmo- globin per cent.	Red cell index	White cells	Finely granular oxyphil	Coarsely granular oxyphil	Lympho- cytes	Hyaline	Others
Sept. 19, 3.30 p.m.	..	1047	5,760,000	72	62	18,600	93.2	..	.7	6.1	
" 4 " "	..	1054.5	5,768,000	67	58	23,200	93.1	.1	2.4	4.4	
" 4.30 " "	98	1055	5,596,000	69	61	26,200	91.2	..	3.8	5	
" 7 " "	..	1053	5,538,000	71	64	30,800	92.5	..	3.7	3.7	.1
" 10.30 " "	98	1053	5,940,000	78	65	43,800	92.8	..	2.9	4.2	.1
" 20, 7.30 a.m.	101	1053.5	5,840,000	82	70	27,600	92	..	4.4	3.6	
" 1.30 p.m.	..	1051	5,604,000	87	77	16,400	91	..	6	3	
" 4.30 " "	100.2	1053	4,616,000	85	91	20,400	91.2	..	4.8	4	
" 21 to 27 Patient maniacal, examination impossible.							One or more myelocytes seen in each count.				
" 28, 4.30 p.m.	99	..	..	..	..	10,625	80.4	2.4	10.6	6.6	
" 29 " "	99	..	..	..	..	12,800	87.1	.5	6.8	5.4	.2
" 30 " "	97.8	..	..	..	..	13,600	81.7	.8	11.5	6	
Oct. 1 " "	98	..	..	..	..	11,400	75.8	1.9	12.4	9.7	.1
" 2 " "	97.6	..	..	..	..	9,800	74.2	2.2	14.1	9.5	
" 3 " "	97.8	..	..	..	..	8,600	77	1.4	14.7	7.2	.3
" 4 " "	98.2	..	..	..	..	14,400	78.3	1.8	10.3	9.3	.3
" 15 " "	98	..	..	..	..	9,000	62.7	3.6	25.7	7.6	.4
						Before the attack	63.8	2.1	22.4	11.5	

TABLE XVI.

CONDITION DURING CONVULSIVE SEIZURES.

Oct. 22, 1901 : 1 p.m.	1 seizure	16 seizures in 9½ hours.
3.15 to 3.35 p.m.	4 seizures	
5.15 p.m.	1 seizure	
5.45 to 6.15 p.m.	2 seizures	
7 to 10 p.m.	6 seizures	
10.45 p.m.	2 seizures	
Early following morning	1 seizure	
Total	17	

		No. of seizures	White cells	Finely granular oxyphil	Coarsely granular oxyphil	Lympho- cytes	Hyaline	Myelo- cytes and others
Oct. 22—								
3.30 p.m.	99.2	4	26,200	77	5	11.7	6	.3
4.15 „	..	5	38,500	81.5	3.7	9.2	5.5	.1
5 „	..	5	28,500	89.9	1.2	5.7	3.2	
5.30 „	..	6	..	86.6	.8	8.6	4	
6.15 „	..	8	27,000	90.5	.9	6	2.6	
10 „	..	14	28,600	90.9	.4	4.7	4	
10.30 „	..	..	..	91.4	.4	4.1	4.1	
11 „	..	16	24,600	90	.1	4.4	5.6	
Oct. 23—								
4.30 p.m.	..	17	19,400	84	.2	11.1	4.2	.5

TABLE XVII.

CONDITIONS DURING CONVULSIVE SEIZURES.

Sept. 27 : Seven strong seizures between 7.30 and 8.30 p.m.

Sept. 28, 2.30 a.m.	38,000	92.2	4	3.8	.1
„ 3.30 „	40,600	92.8	3.9	3.2	
„ 7.30 „	34,000	92.6	3	4.4	
„ 12.30 p.m.	32,400	93.5	3.5	3	

Patient died at 3.40 p.m.

At 2.30 a.m. the blood was very dark and viscid.

	Specific gravity.	Red cells.	Hæmoglobin.	Red cell index.
At 7.30 a.m.	1056 ..	5,320,000 ..	77 ..	.72

TABLE XVIIa.

CASE II. TABLE XVI.

Six Seizures, 11.30 a.m. and 12.30 p.m.

	White cells per c.mm.	Finely granular oxyphil	Coarsely granular oxyphil	Lympho- cytes	Hyalines	Myelocytes
1.30 p.m.	25,300	87.6	..	6.3	5.8	.3
2.15 ..	29,800	92.1	..	4.5	3.2	.2
Normal count ..		53.3	2.7	33.7	10.3	

TABLE XVIIb.

CASE II. TABLE XVII.

Three Severe Seizures at 9.45 a.m.

	White cells per c.mm.	Finely granular oxyphil	Coarsely granular oxyphil	Lympho- cytes	Hyalines	Myelocytes
10.30 a.m.	12,800	86.4	.1	6.7	6.8	
1 p.m. ..	19,400	90.3	..	5.6	4.1	
One or two myelocytes seen in each count.						
Normal count ..		60.5	3.7	22.4	12.3	Basophil .1

TABLE XVIII.

EXAMINATION OF A CASE OF "STATUS EPILEPTICUS," IN WHICH A PATIENT
HAD 32 FITS BETWEEN 9.30 A.M. AND 11.15 A.M.

	Tem- perature	Number of fits	White cells per c.mm.	Finely granular polymor- pho- nuclear	Eosino- phils	Lympho- cytes	Hyaline	Myelo- cytes
Oct. 8—	Degrees							
10.15 a.m.	98.2	13	18,700	41.8	5.2	41.1	11.2	.7
10.45 ..	..	24	21,200	49.3	3.5	28.6	18	.6
11.15 ..	..	32	21,600	56.2	4.2	29	10	.6
11.45 ..	..	..	21,800	83.7	1	8.5	6.5	.3
12.15 p.m.	100.6	..	27,800	85.6	1.2	6	6.5	.6
1.15 ..	..	..	28,400	85	.6	9.4	5	
3.15 ..	..	..	11,700	87.8	.3	7	4.6	.3
10.15 ..	101	..	12,900	55	.4	31.4	12	.2
Oct. 9—								
11 a.m.	98.8	..	..	78.6	1	6	14	.4
Oct. 10—								
11 a.m.	97.8	..	10,400	69.1	5.3	11.6	14	
Oct. 15—								
11 a.m.	98	..	14,600	61	6.6	17	15	.4
Count taken before the status			7,410	65.8	6.8	16.5	10.6	Basophil .2

CASE OF FRIEDREICH'S DISEASE, WITH
AUTOPSY AND SYSTEMATIC MICROSCOPI-
CAL EXAMINATION OF THE NERVOUS
SYSTEM.

By FREDERICK W. MOTT, M.D., F.R.S.

SUMMARY.—*Weakness in the legs commenced at 16, and gradually progressed until he became incapacitated; in consequence dejected, with a tendency to suicidal impulses, for which, at the age of 36, he was sent to the asylum from the infirmary. Physical condition on admission typical. Scoliosis, talipes equinus and pes cavus, paresis, absence of deep reflexes, no affection of cutaneous sensibility, normal pupils, superficial reflexes present, muscular incoördination, speech defect. Death twelve months later of cardiac failure. Naked eye wasting of the upper part of the cerebral convolutions, atrophy of Betz cells, thinning of ascending parietal cortex, some diffuse sclerosis of internal capsule and pyramidal tract in crus cerebri, very marked sclerosis of the pyramidal systems, crossed and direct in the medulla and spinal cord. Degenerative atrophy of dentate nucleus, sclerosis of the direct and ventral cerebellar tracts, atrophy of the cells of Clarke's column. Atrophy and disappearance of many cells of the spinal ganglia, marked outfall of the coarse fibres of the posterior roots and their fibre extensions into the cord to form the (a) root zone, (b) the plexus around cells of Clarke's column, and (c) the long tracts of the posterior column which go to Goll and Burdach's nuclei. Integrity of the fine root fibres and Lissauer's tract. A corresponding change found in the peripheral nerves; there is a great outfall of coarse fibres and integrity of fine fibres, especially marked in the nerves of the lower limbs. Degeneration of sensory nerves of muscle; the muscles, although wasted, show a fairly normal striation, the anterior horn cells and anterior roots are intact. Con-*

clusion : That this case affords an excellent pathological proof of the neurone doctrine, as the only explanation is a progressive and physiologically selective degeneration of systems of neurones functionally correlated but anatomically widely separated.

W. W., admitted October 12, 1903. Aged 36. Single. Occupation, a plumber. No other notes than the admission order were obtainable, as he had no friends and was not visited.

The certificate states that he is feeble-minded, and at times speaks of using a knife on himself. He makes rambling statements. The patient has attempted to cut his throat.

Dr. Jones kindly asked me later on to see the case, and I have made the following notes from the case-book and my own observation. I diagnosed the case as Friedreich's disease, requesting Dr. Watson, my late assistant, to preserve the material if the patient died.

Mental state.—He answers questions rationally without confusion, comprehending all that is said to him. He states that for more than fourteen years he has been gradually losing power, and finally became quite incapacitated and had to go into the infirmary. Questioned as to his attempt to commit suicide, he admits that he had a knife in his mouth, and the nurse thought he meant to commit suicide. He states that he felt very miserable on account of his helpless condition. It is somewhat difficult to maintain his attention, but his memory is fairly good for recent and remote events in his life. He has a fair idea of time and place, and there are no illusions, hallucinations or delusions discoverable. His speech is slurred and somewhat difficult to understand, dentals and sibilants being especially affected. Apart from the suicidal tendency, and a certain degree of mental feebleness, there is no evidence of insanity.

Physical condition.—There is well-marked scoliosis and talipes-equinus and pes cavus. The physiognomy lacks expression, and there is general muscular wasting and incoördination.

The tongue is tremulous, and deviates to the right on

protrusion. The pupils are equal and react to light and accommodation.

There is no organic disease of the heart or lungs discoverable. He is bed-ridden now, as he is unable to walk or stand.

Upper limbs.—All the small muscles of the hand are wasted, especially the muscles of the thenar and hypothenar eminences and the interossei. There is a general loss of tone and strength of all the muscles, and there is no wrist tap or triceps contraction. The grasp is feeble and coördination is markedly impaired. Sensibility to pain, touch and temperature normal. There is no paræsthesia or painful sensations.

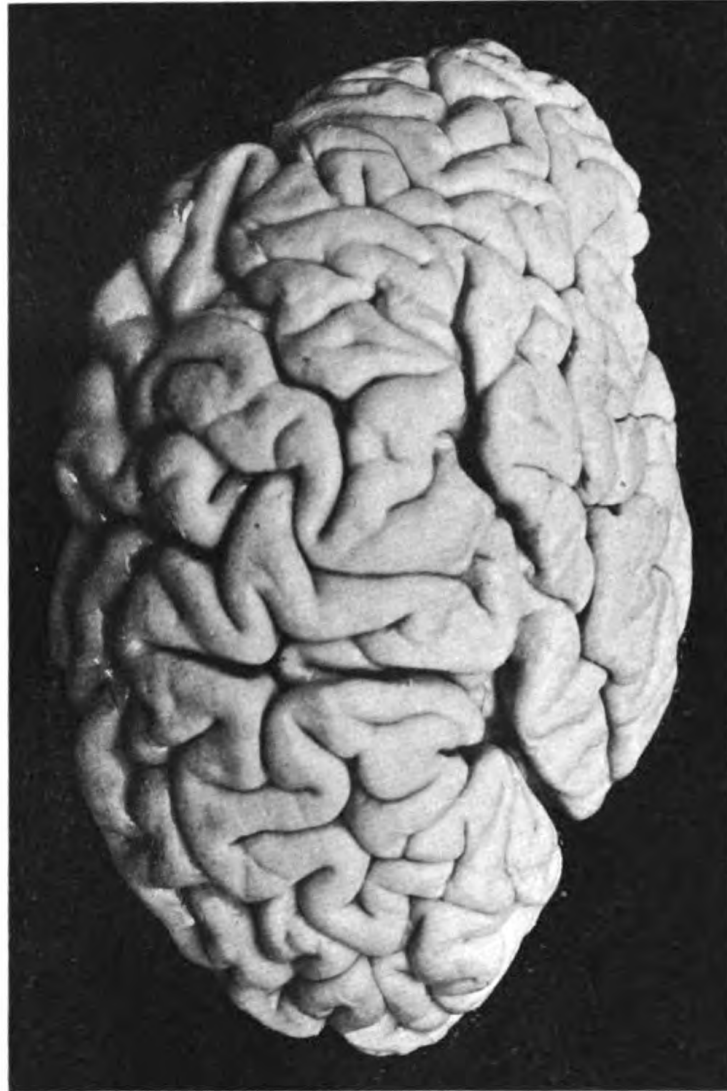
Lower limbs.—There is marked atrophy of all the muscles; there is talipes-equinus and pes cavus.

Deep reflexes all absent; superficial reflexes present. Sensibility to pain, touch and temperature sensations unaffected. Mechanical irritability of muscles, especially of the right calf. There is no loss of control over bladder or rectum, but occasionally he suffers from some slight incontinence of urine. This is possibly due to his helpless condition.

January 27, 1905. "Patient died this morning from cardiac and respiratory failure resulting from ascending paralysis." Case Book note.

Autopsy (made by Dr. G. Watson, January 28, 1905).—Nutrition, good. Physique, average. Rigidity, passing off. Muscular system, fair. *Post-mortem*: Lividity on dependent parts. Deformities, &c., well marked scoliosis with convexity to right, well marked pes cavus both sides. Apparent talipes equinus and some genu valgum. Chest, large. Upper part of body well developed as compared with lower. Pelvis, narrow. Signs of degeneracy, &c. Teeth, very good. Nose, good. Palate, rather high but not narrow. Skull, somewhat dense in frontal region. Pupils slightly irregular, right 4 mm., left 3 mm. Dura mater, natural, subdural space, fluid in large excess, no deposit. Pia-arachnoid, slight thickening, F. P., very little opacity, congested, slight mid-line prefrontal adhesions, strips very readily. Sub-arachnoid space, fluid in excess. Vessels, natural or very slightly thickened. Sinuses, empty. Weight of brain, 1,235 grams. Right hemisphere 535 grams, left hemisphere 535 grams, stripped 508

PLATE II.



Left hemisphere, Friedreich's disease, stripped of its membranes. Observe the atrophy of the upper half of the central convolutions. Note the deep, wide dark sulci in this region as compared with other regions. Reduction $\frac{1}{3}$.

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grams, loss equals 27 grams. Cerebellum, pons and medulla, 145 grams, 145×8 equals 1,160. The cerebellum pons, and medulla are therefore under the normal proportional weight to the whole brain. Convolutions, about average, gyri rather large in prefrontal, smaller in parietal lobules, no general or local softening. Slight general wasting in prefrontal, *little or none elsewhere, but there appears to be some under development or wasting of the upper quarter of the ascending parietal and frontal and of the hinder part of first frontal (left side only stripped)*. Brain preserved for microscopical examination (vide photograph, plate ii.). Fourth ventricle, a few fine granulations in lateral sacs only. Cranial nerves, apparently natural. Spinal cord, removed for microscopical examination. Peripheral nerves, many removed for microscopical examination.¹ Thyroid gland, rather larger than natural. Bronchi, congested. Right lung, two dense depressed scars near apex, a firm nodule at middle of anterior border of middle lobe. Nodule the size of a cherry and contains some dense cheesy material. Posterior portions of upper and lower lobes consolidated (hypostatic). Weight 620 grams. Left lung, 600. No scar at apex. Hypostatic consolidation of posterior portion and base. Heart, considerably enlarged, especially left side. Weight 475 grams. Left ventricle and auricle: ventricle much dilated, walls friable, auricle dilated; right ventricle and auricle somewhat dilated, contains much p. m. and a little a. m. clot. Valves, all quite natural. Aorta, a few scattered specs of early atheroma. Liver, 970 grams, congested and somewhat fatty, nutmeg. Gall bladder, bile inspissated, five large darkly pigmented stones, duct obstructed. Spleen, 120 grams, density increased. Right kidney, 130 grams, left kidney, 110 grams, density much increased; two or three depressed scars on surface of each kidney, apparently the remains of old surface cysts, organs congested, cortex and medulla, natural thickness, capsule natural. Abdominal aorta, as thoracic. Adrenals, cystic, very little medulla, right equals 5.12 grams, left equals 4.25 grams. Stomach, some catarrh and moderately intense congestion. Small intestine, fairly intense congestion of duodenum, patchy congestion (moderate) of ilium. Large intestine, some patchy congestion, not marked, contents solid. Bladder natural, urine by catheter, a thick cloud of albumen. Penis, very large, no scar. Inguinal glands, natural. Cause of death (a) Immediate cardiac failure, cardiac dilatation, hypostatic pneumonia; (b) other pathological

¹ The material was placed in the hands of Dr. Fenton who however, had not time to do more than cut up the material systematically and make a few sections. The investigation has been mainly carried out by myself. Unfortunately the medulla and pons have not yielded very satisfactory sections.

conditions, obsolescent tuberculosis of lungs, and chronic Bright's disease.

The Microscopic Examination of the Nervous System.

Method.—The brain and spinal cord. Various portions of the brain and spinal cord were hardened in formalin, and subsequently embedded in paraffin. Sections of 10 μ thickness were cut and stained by Nissl's method with polychrome and methylene blue dyes, also polychrome and eosin. The remainder of the brain and spinal cord and nerves and muscles were hardened in Müller's fluid, in order that sections might be cut to display the fibres to advantage.

Description of histological changes.—Sections of the motor cortex, namely, of the ascending frontal and ascending parietal convolutions were taken at five different levels, in such a way as to include the superficial part of each convolution, and the whole of the intervening grey matter of the fissure of Rolando.

(1) *The top of the ascending frontal and ascending parietal, close to mesial surface.*—In both cases the grey matter of the cortex is considerably thinner than natural, and stains imperfectly (*vide* fig. 1, plate iii.) All the layers seem to be thinner than normal. Examined with an oil immersion the polymorphic layer of cells shows marked changes. They are greatly diminished in numbers, those that remain are for the most part badly stained or have crumbling edges; and there is a great proliferation of glia cells, but only the nuclei are seen, and there is but little cell protoplasm and no branching processes. These glia cells are in clumps of from two to twelve, sometimes in spaces, sometimes around vessels or in the perivascular spaces. The small arteries are markedly changed, especially in the deeper layers of the cortex, where the hyaline degeneration in many of the transected vessels appears to be so marked as to almost obliterate the lumen. The nuclei in these vessels are faintly stained, and very numerous. The vessels are only visible by a faintly stained outline. The rest of the wall is often seen thrown into folds of a pale amorphous unstained material. In the more

parietal (1), and ascending frontal (2). The drawing was made from the summit of two sections of convolutions shown in fig. 1, plate I. The ascending parietal shows a diminution of cells and the large flask-shaped cells are absent. In the ascending frontal the large Betz cells are absent. Magnification 120. By the side of each layer is the typical cell magnified 300.

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superficial parts of the cortex there is a nuclear proliferation in the vessel walls, and the nuclei often have a granular degenerative appearance. The degenerative appearance of the vessels resembles (but is not nearly so intense), the degenerative appearance of the vessels (*vide* fig. 2, plate i.) in the corpus dentatum of the cerebellum. Careful search of a large number of specimens exhibited *no giant Betz cells*. Occasionally a medium sized Betz cell was found (*vide* comparative measurements). The ascending parietal showed a corresponding diminution of cells (*vide* fig. 1, plate iii.), only occasionally could I find a large infra-granular pyramidal cell. Examination of this region for fibres showed a corresponding diminution of fibres; and especially a disappearance of the coarse fibres found in these regions.

(2) *Top of ascending frontal and parietal, opposite lower border of first frontal* showed the same appearances as in the last-named, but less marked. A certain number of fairly well-formed medium-sized Betz cells were seen, but no giant Betz cells. A few small and medium-sized Betz cells appeared to be undergoing atrophic degeneration.

(3) *Central convolutions opposite base of second frontal, including the annectant buttress*.—Examination very similar to the last.

(4) *Central convolutions just below the genu*.—Cells of the cortex more numerous. A few medium and some large Betz cells seen at the bottom of the fissure.

(5) *Central convolutions opposite base of third frontal*.—Small Betz cells numerous, and the cortex thicker and possessed of more cells than in the other regions before-mentioned.

FRIEDREICH'S DISEASE. BETZ CELLS.

Top of Ascending Frontal.— $45\ \mu \times 20\ \mu$, $40\ \mu \times 20\ \mu$, $45\ \mu \times 15\ \mu$, $50\ \mu \times 15\ \mu$, $40\ \mu \times 25\ \mu$, $50\ \mu \times 20\ \mu$, $50\ \mu \times 20\ \mu$, $30\ \mu \times 15\ \mu$, $45\ \mu \times 20\ \mu$, $25\ \mu \times 30\ \mu$, &c.

Top of Ascending Frontal, Right Side (from Nissl stained specimen).— $55\ \mu \times 30\ \mu$, $55\ \mu \times 25\ \mu$, $35\ \mu \times 25\ \mu$, $35\ \mu \times 25\ \mu$, $40\ \mu \times 25\ \mu$, $55\ \mu \times 35\ \mu$, $60\ \mu \times 15\ \mu$, $25\ \mu \times 20\ \mu$, &c.

Top of Ascending Frontal, Right Side (drawn).— $40\ \mu \times 20\ \mu$ ($70\ \mu \times 15\ \mu$? pyramid), $40\ \mu \times 20\ \mu$, $57\ \mu \times 20\ \mu$, $40\ \mu \times 20\ \mu$, $60\ \mu \times 20\ \mu$, &c.

Top of Ascending Frontal (Friedreich).— $40\ \mu \times 20\ \mu$, $40\ \mu \times 25\ \mu$, $45\ \mu \times 25\ \mu$, $50\ \mu \times 20\ \mu$, $45\ \mu \times 25\ \mu$, $40\ \mu \times 20\ \mu$, $50\ \mu \times 30\ \mu$, $50\ \mu \times 20\ \mu$, $35\ \mu \times 15\ \mu$, &c.

Ascending Frontal, Opposite Base Third Frontal.— $40\ \mu \times 20\ \mu$, $30\ \mu \times 20\ \mu$, $30\ \mu \times 20\ \mu$, $40\ \mu \times 25\ \mu$, $45\ \mu \times 25\ \mu$, $35\ \mu \times 25\ \mu$, &c.

TETANUS. BETZ CELLS.

Junction of First Frontal with Ascending Frontal.— $85\ \mu \times 20\ \mu$, $50\ \mu \times 20\ \mu$, $55\ \mu \times 30\ \mu$, $45\ \mu \times 35\ \mu$, $70\ \mu \times 45\ \mu$, $75\ \mu \times 35\ \mu$, $60\ \mu \times 30\ \mu$, &c.

N.B.—There are no "giant" cells in the Friedreich specimens, measuring between $70\ \mu$ and $80\ \mu$, as in Tetanus; the largest Betz cells in the Friedreich measuring between $45\ \mu$ and $55\ \mu$.

FRIEDREICH'S DISEASE. LARGE CELLS IN THIRD LAYER OF ASCENDING PARIETAL.

Top of Ascending Parietal, Right Side (polynuclear Basophils, Eosinophils).— $40\ \mu \times 15\ \mu$, $35\ \mu \times 15\ \mu$, $40\ \mu \times 10\ \mu$, $35\ \mu \times 10\ \mu$, $50\ \mu \times 15\ \mu$, $50\ \mu \times 15\ \mu$, &c.

Top of Ascending Parietal, Right Side (Nissl).— $50\ \mu \times 15\ \mu$, $45\ \mu \times 10\ \mu$, $45\ \mu \times 15\ \mu$, $30\ \mu \times 15\ \mu$, $35\ \mu \times 10\ \mu$, $40\ \mu \times 10\ \mu$, $45\ \mu \times 10\ \mu$, $40\ \mu \times 15\ \mu$, $35\ \mu \times 20\ \mu$, $40\ \mu \times 25\ \mu$, $35\ \mu \times 10\ \mu$, $35\ \mu \times 10\ \mu$, $45\ \mu \times 10\ \mu$, $60\ \mu \times 11\ \mu$, $50\ \mu \times 15\ \mu$, &c.

Top of Ascending Parietal, Opposite Bottom of First Frontal Convolution.— $50\ \mu \times 15\ \mu$, $35\ \mu \times 15\ \mu$, $50\ \mu \times 20\ \mu$, $35\ \mu \times 15\ \mu$, $45\ \mu \times 15\ \mu$, $35\ \mu \times 15\ \mu$, $40\ \mu \times 15\ \mu$, $45\ \mu \times 10\ \mu$, $50\ \mu \times 10\ \mu$, &c.

TETANUS. LARGE CELLS IN THIRD LAYER OF ASCENDING PARIETAL.

Junction of Superior, Middle Third of Ascending Frontal Parietal (polynuclear).— $60\ \mu \times 15\ \mu$, $60\ \mu \times 10\ \mu$, $50\ \mu \times 15\ \mu$, $75\ \mu \times 10\ \mu$, $50\ \mu \times 15\ \mu$, $50\ \mu \times 15\ \mu$, $50\ \mu \times 10\ \mu$, $35\ \mu \times 15\ \mu$, $45\ \mu \times 10\ \mu$, $55\ \mu \times 15\ \mu$, $60\ \mu \times 10\ \mu$, $60\ \mu \times 10\ \mu$, $55\ \mu \times 10\ \mu$, $60\ \mu \times 15\ \mu$, &c.

Junction of Superior, Middle Third of Ascending Frontal Parietal (Nissl).— $75\ \mu \times 15\ \mu$, $70\ \mu \times 15\ \mu$, $45\ \mu \times 15\ \mu$, $40\ \mu \times 20\ \mu$, $70\ \mu \times 15\ \mu$, $50\ \mu \times 15\ \mu$, $45\ \mu \times 10\ \mu$, $35\ \mu \times 25\ \mu$, $60\ \mu \times 15\ \mu$, &c.

N.B.—In Friedreich the largest cells measure from $45\ \mu$ to $50\ \mu$; in Tetanus the largest cells measure from $60\ \mu$ to $75\ \mu$.

Summary.—An examination of a large number of sections revealed the almost complete absence of the giant Betz cells, and some diminution of the medium-sized Betz cells in the leg, arm, face, jaw and lingual areas of the cortex; a general atrophy of the pyramidal and polymorph layers, causing a diminution of the cortex, without a corresponding glia proliferation. In the ascending parietal in the same regions there was a diminution of all the layers, and a comparative diminution of the large pyramids. By the fibre method there was a decided diminution of the

large coarse fibres in the ascending frontal in its upper third, and probably a diminution, though less evident, of coarse fibres in the ascending parietal.

Examination of the internal capsule showed a slight diffuse sclerosis in the posterior half; likewise a slight diffuse sclerosis was found in the crus cerebri in the region corresponding to the motor path. This was much more obvious in the pyramidal systems of the pons and medulla. In these latter structures there was also a distinct sclerosis of the antero-lateral tract and its continuation upwards; also of the restiform body. The optic thalamus showed no recognisable changes, but a complete and systematic examination of this structure was not undertaken.

Cerebellum.—When the lateral lobe of the cerebellum was cut through a naked eye atrophy of the corpus dentatum was observable. Sections of the corpus dentatum and the white matter continuous with it exhibited the following changes. Marked degenerative atrophy of the large cells of the corpus dentatum; not a healthy normal cell could be seen. Some of the cells were represented only by a little pigmented protoplasm. In other places the cells had obviously disappeared; while in places where the cells remained and possessed branching processes, they were evidently in a state of necrobiosis, for the protoplasm was uniformly stained a dull pinkish purple colour (polychrome and eosin) (fig. 3, plate i.). In those regions where the atrophy and destruction were most marked, profound vascular changes, of quite an ancient character were found. The capillaries were numerous in these regions, but they were evident, not by the blood contained in them, but by small round purple staining particles of degenerated material. The walls of the larger vessels also contained these degenerated granules (see fig. 4, plate i.). The staining reaction is that of calcarous degeneration of very old standing. The white matter which runs into the dentate nucleus, examined under a low power, is seen to contain a large number of dilated vessels, the perivascular sheath and walls of which contain these granules. There is considerable atrophy of the nerve fibres. Examination of

the cortex of the lateral lobe showed in places atrophy of the cells of Purkinje, and commencing degenerative change. This, however, was not by any means universal, but only in places.

Medulla and pons.—I was unable to discover any atrophy of the motor nuclei, or of Deiter's nuclei. There appeared to be some sclerosis of the ventral branch of the eighth, and atrophy of the fibres about Deiter's nucleus. Of this, however, I am not certain. There is a well-marked atrophy of the fine plexus of fibrils of Goll's and Burdach's nucleus. There is no atrophy of the posterior longitudinal bundle or sclerosis. There is no change in the fillet. The red nucleus was, unfortunately, not examined.

Spinal cord.—The spinal cord is much smaller than that of a normal adult.

Examination of the anterior and posterior roots in the regions in which the sections of the cord were examined.

First and second sacral, with roots of cauda equina. All the posterior roots show a marked sclerosis, but every root contains, under examination of the high power, numbers of fine medullated fibres, but very few or no coarse fibres (*vide* photomicro, fig. 1, plate iv.). This statement applies practically to the condition of the posterior roots from the fifth or sixth cervical downwards. It is of interest, when we come to consider the degeneration in the afferent systems of the spinal cord. At all levels the anterior roots appear to be normal.

Spinal cord.—The cells of the anterior horn at all levels appear to be normal, or to show only recent chromolytic changes. In no region of the spinal cord could any cells of Clarke's column be found; and this corresponds with the facts that there is a complete sclerosis of the ventral and dorsal cerebellar tracts. There is, moreover, a complete sclerosis of the crossed pyramidal tract in the cervical, dorsal and lumbar regions, but the degeneration in the direct tract is not very marked; it is more obvious on one side than the other, and is best seen in the upper dorsal region. It extends down to the eighth or ninth dorsal. The whole cord is very much shrunken, and there is an indentation in

PLATE IV.



FIG. 1.

Section of a posterior rootlet with fine fibres entering to form Lissauer's tract ; internal to this is the sclerosed posterior column.

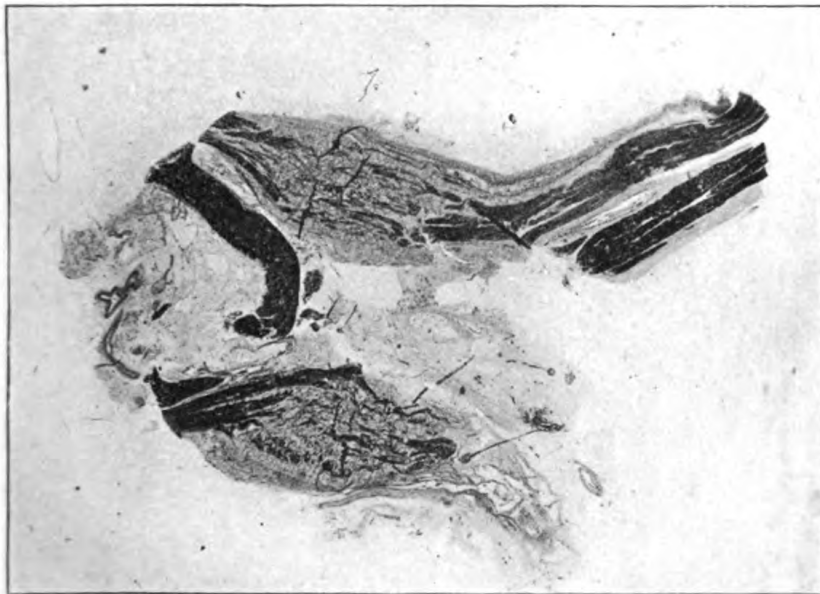


FIG. 2.

Posterior spinal ganglion cut in half. The two halves are shown with the dark well-stained anterior root above and the unstained posterior root below.

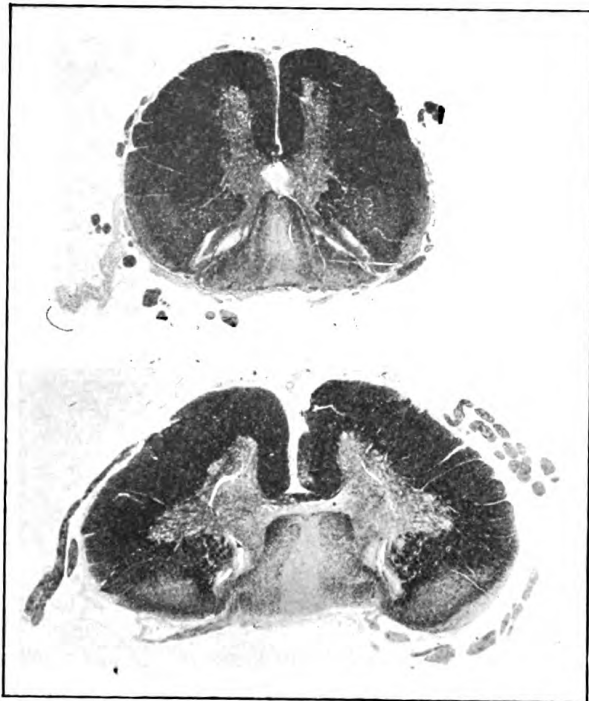


FIG. 1.—Sections of 2nd cervical and 6th cervical segments. The degeneration of the posterior root fibres has practically ceased in the uppermost of these two segments. The degeneration in the crossed pyramidal tract is less obvious owing to the fact that the psycho-motor neurons supplying the lower limbs and trunk are much more affected.

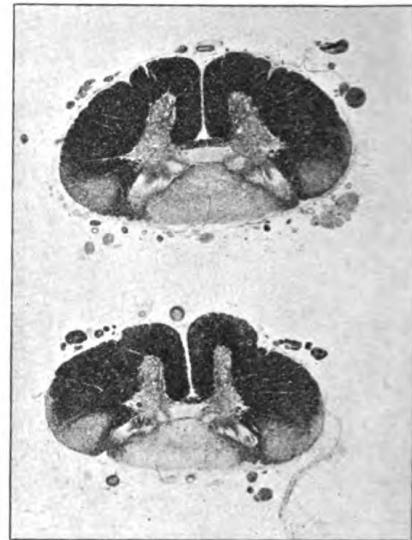


FIG. 3.—Sections of the 6th (lower) and 9th dorsal segments. Observe now the additional degenerated cerebellar tract, the existence of a well-stained Lissauer's tract, pale unstained middle third of the posterior horn, and an absence of a film plexus in Clarke's column, causing it to appear pale and unstained.



FIG. 4.—Sections of the 2nd and 5th lumbar segments. Note in the latter the unstained posterior roots as compared with the anterior, the sclerosis of the crossed pyramidal tracts and the posterior columns, except the endogenous system in the latter. Observe that there is no obvious meningeal thickening. Observe the absence of staining in the middle third of the posterior horn corresponding to the root zone.

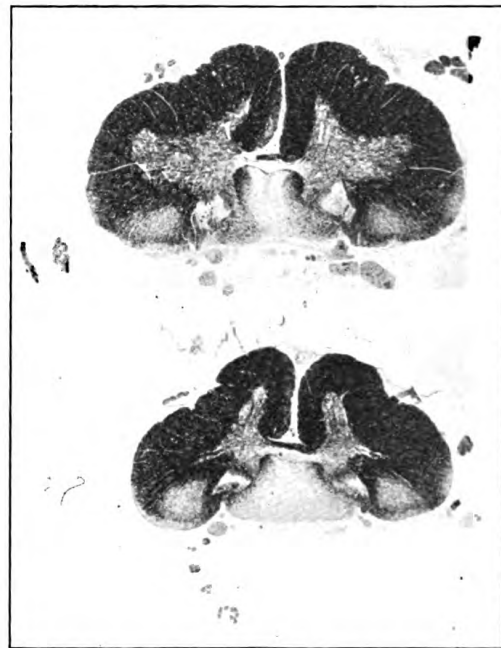


FIG. 2.—Section of 6th cervical (upper) and 1st dorsal. Observe that as in tabes dorsalis the degeneration atrophy of the posterior column and posterior roots become less marked in the upper part of the cervical enlargement. The degeneration is just visible in the direct tract of one side in the uppermost section. Microscopically examined it can be observed on both sides though unequal in degree.

the antero-lateral region in the dorsal portion of the cord, and this is probably, in great measure, due to the drawing in, occasioned by sclerosis of other parts of the cord. The most marked atrophy is in the posterior column. There is a complete sclerosis of Goll's column up to the nucleus funiculus gracilis, and a very extensive sclerosis of Burdach's column, the former corresponding to the leg, trunk fibres, the latter to the upper limb fibres proceeding to the posterior column nuclei. But all the way down, the endogenous systems of fibres of the posterior column are apparent, terminating below in the median oval area of Fleschsig, and the posterior triangle in the lowest sacral region. The exogenous fibres of the posterior column that are atrophied are (1) the fibres which form the root zone of Charcot; (2) the fibres which go to Clarke's column; (3) the fibres which ascend in the posterior median, and postero-external column to Goll and Burdach's nuclei. The fibres which are not atrophied are those of Lissauer's tract. These are the fine fibres which we saw were present in all the posterior roots. In the lumbo-sacral regions there are indications of a congenital defect in the spinal cord. The central canal is large and dilated. It has an embryonic shape, and is surrounded by a large amount of glia tissue, which is continuous, with two or three oval spaces along the median fissure, as if complete obliteration of the original medullary cavity had not occurred. There is very little thickening of the membranes, or indication of an inflammatory change having been the cause of the degenerative atrophy and subsequent sclerosis; but there is a glia proliferation around and filling up the central canal throughout the cord (*vide* plate v., figs. 1, 2, 3, 4).

Posterior roots and spinal ganglia.—The roots of the cauda equina were tied together with the filum terminale, embedded in celloidin, and sections were cut and stained by Weigert and Pal methods; all the posterior roots were found sclerosed and exhibited a marked contrast to the healthy stained anterior roots (*vide* photomicrograph, fig. 2, plate iv.). The following posterior spinal ganglia were examined by Nissl and Weigert methods for cells and fibres, the fifth

PLATE I. FRIEDREICH'S DISEASE.

Fig. 1. Section of top of ascending frontal and ascending parietal. The ascending frontal has a > in the anterior border: the ascending parietal shows a thinner layer of cortical grey matter than the ascending frontal, but in both it is diminished. Magnification 8×1 .

Fig. 2. Small degenerated vessels in the deeper layers of the cortex of this region especially observable in the situation which should be occupied by the giant Betz cells on the mesial border and surface of the ascending frontal. Magnification 500.

Fig. 3. Types of large cells still existent in the degenerated and atrophied corpus dentatum. Magnification 500.

Fig. 4. A small vessel with calcareous degeneration of its wall seen in longitudinal section, a larger vessel seen in transverse section. Magnification 500.

Fig. 5. Small portion of a longitudinal section of the eighth cervical ganglion. Practically only one cell would pass as perfectly normal. Some of the cells are obviously shrunken and atrophied (*a*); others show a marked chromatolysis and the nucleus is not seen, owing to its eccentric position it is more readily cut off by the section; where the cells are atrophied or absent there is an interstitial and endothelial proliferation. Magnification 300.



lumbar, the second lumbar, tenth dorsal, fourth dorsal, first dorsal, and fifth and eighth cervical. When the spinal cord was removed from the body it was observed that the lumbo-sacral ganglia were much smaller than normal, and the corresponding posterior roots thin, flattened and greyish-white in colour.

All the above mentioned spinal ganglia showed change microscopically.

A comparison of the staining of the myelin sheaths of the anterior and posterior roots as they lie side by side upon the latter entering and leaving the ganglion, leaves no doubt of an appreciable outfall of the large sensory fibres, their place having been taken by dense fibrous tissue. There are still, however, as the photograph shows, a number of myelinated fibres in the ganglion and the degenerative atrophy of the afferent proto-neurons becomes less marked the higher the segmental ganglion examined. It can be observed quite easily with a hand lens in the lumbo-sacral region, but requires a microscope in the upper dorsal and cervical regions. The fibres that persist in the posterior roots are mainly the small finely medullated fibres, but there are a few large coarse fibres in many of the rootlets. The fine fibres as the photograph shows run directly into Lissauer's tract which contains a great wealth of fibres. It was observed by Pal and Weigert staining that a great number of the large cells were stained all over by fine purple dots. I take this to indicate a fatty degeneration suggestive of slow necrobiosis. The small and medium sized cells did not show this change, but by Weigert method were stained brown.

By Nissl method.—The following posterior spinal ganglia were examined: seventh cervical, seventh dorsal, fourth lumbar.

Eighth cervical.—The small cells as a general rule are more deeply stained. None of the large cells show a proper amount of chromophilous material; the majority are very pale. Many cells contain a large amount of yellow pigment at the pole, and in some cases occupying nearly half the cytoplasm. The large cells are often distorted in shape

and vacuolated or broken up into an irregular amorphous material. When the cells are atrophied or destroyed there is a proliferation of the endothelial cells of the capsule and interstitial fibrous tissue. The nucleus is generally speaking in the centre of the cell, the nucleolous and nuclear membrane being imperfectly stained (*vide* fig. 5, plate i).

Seventh dorsal.—The ganglion shows similar changes to those above described, probably more cells show a pigmentary degeneration than in the cervical region.

Third lumbar.—The same change can be observed, but more extensive and advanced.

Not only does the spinal cord appear small like that of a child, but also the spinal ganglia. Some of those in the lower dorsal and lumbo-sacral regions are obviously considerably diminished in size.

Peripheral nerves and muscles.—The following nerves and muscles were examined. The sciatic, popliteals, anterior and posterior tibials, musculo-spiral and ulnar, hypothenar and thenar muscles, and interossei of hand; some small muscles of foot and tibialis anticus.

All the peripheral nerves showed a great outfall of the coarse fibres and integrity of the fine fibres, as in the posterior roots. This atrophy was most marked in the nerves of the lower limb. The sciatic nerve was of a fair size in transection, but there was more fibrous tissue than nervous tissue in its composition; the epineuron, perineuron, and endoneuron were all increased (*vide* photomicrograph, fig. 1, plate vi.). This statement holds true also of the other nerves examined. By Marchi method no recently degenerated fibres were found.

Examination of any bundle with a high power exhibited a great diminution of the coarse fibres. Those that are present are doubtless nearly all motor efferent. A large number of fine medullated fibres, similar to those seen in the posterior roots, exist. Many of these are vaso-motor efferent and afferent, but some may be cutaneous (*vide* photomicrograph). The muscles for the most part exhibited fibres with well-defined striation; myelinated nerves were found in them, but the bundles were only partially filled with fibres (*vide* photomicrograph, fig. 2, plate vi.).

PLATE VI.

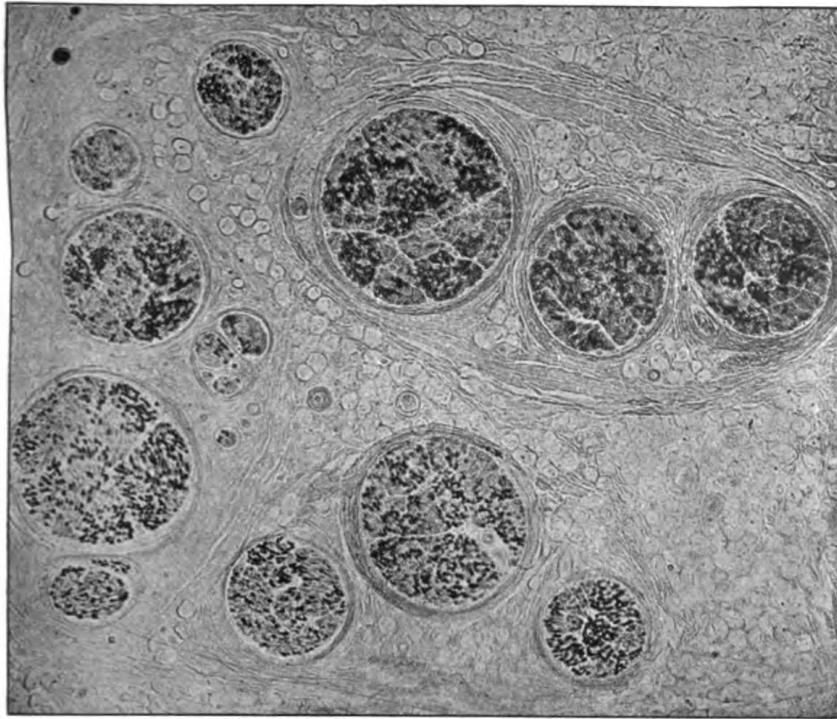


FIG 1.

Small portion of transection of sciatic nerve. The outfall of fibres indicated by pale coloration is much more obvious in some bundles than others. There is a great increase of interstitial fibrous tissue. Magnification 30.

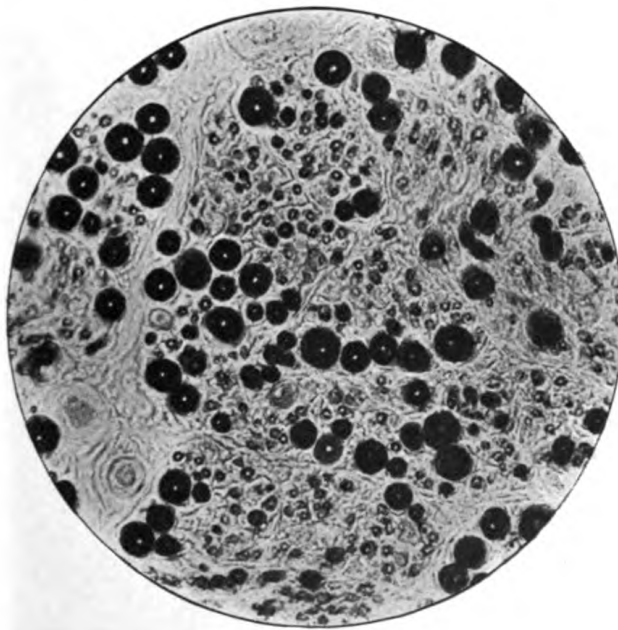


FIG. 2.

A small portion of one bundle more highly magnified, showing paucity of coarse fibres, but abundance of fine fibres with great excess of interstitial endoneurium. Magnification 500.

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Nerves in muscle.—The examination of the following muscles was made by Weigert, Weigert-Pal with counter-staining by borax carmine: muscles of hallux, tibialis anticus, biceps thenar, hypothenar and interossei muscles. Sections were cut parallel and transverse to the long axis of the muscles.

The appearance of bundles of nerves entering the muscle presented a similar appearance to the bundles entering into the formation of the nerve trunks described. There was an obvious outfall of fibres and replacement by dense fibrous tissue. In the muscle itself the microscopic bundles of fibres, containing several fibres to a dozen, varied considerably in respect to the number of transected fibres seen in bundles of comparative equal size. We may, therefore, presume that a number of fibres had disappeared. For the most part the muscle fibres had a normal appearance; but here and there, especially in the muscles of the lower limb which were examined, the fibres had lost their striation. In places where there was obviously degenerated or atrophied nerve fibres there was a considerable nuclear proliferation of the neurilemma and sheath of Henle. This was very evident in sections counterstained with carmine. Often this nuclear proliferation, without any evidence of medullated fibres could be seen to end in a transection of one or more spindles. In fact the spindles were frequently in pairs, and sometimes triplets, as Sherrington has shown to occur in the monkey and cat. Sometimes the transection of the spindle would show several muscle fibres apparently normal in appearance contained in the capsular sheath which also appeared normal, but it was very rare (in a large number of specimens examined) that I found any medullated fibres associated with these spindles in the muscles. Sometimes there was nothing left of the spindle except the sheath, the interior being filled with amorphous granular material (*vide* photomicrographs, figs. 1 and 2, plate vii.). Sherrington has kindly sent me photographs of transections of the spindles and nerves entering muscles after cutting anterior roots, and after removing posterior spinal ganglia in the cat and

the monkey, and I have used these for comparison. His valuable experiments showed that the nerves of muscle derive large numbers of their fibres from the spinal ganglia. In the limb muscles of the monkey and cat he found from a half to a quarter of all the nerve fibres to be sensory. "These sensory fibres end in end organs, muscle spindles, Golgi organs, modified Pacini organs, Pacini organs."—Sherrington.

The motor nerve fibres of skeletal muscle are as a rule larger than the sensory fibres; the sensory nerve fibres in the spindles are larger fibres than the motor.

The tendon bundles of the spindles enter with special frequency into Golgi organs. Unfortunately I am not in a position now to examine the tissues for Pacinian corpuscles and tendon organs of Golgi, but it is reasonable to assume that the nerves of all these end organs which play such an important part in the kinæsthetic functions have undergone partial or complete degeneration in proportion to the outfall of sensory fibres supplying the deep structures. This would fit in with the clinical facts, and the degeneration and sclerosis of the posterior roots and posterior columns, where we have seen that the coarse fibres have in great measure disappeared, whereas the fine fibres entering Lissauer's tract persist almost untouched by the degenerative process. Anderson, in a thesis as yet unpublished, has given evidence to show that the fine fibres subserving skin sensibility are myelinated at a different period to the coarse fibres supplying the deep structures. These muscle spindles may have special functions; by virtue of the intrafusal muscle fibres, they possess contractility, and it is conceivable that they signal active movements rather than passive.

Sherrington,¹ in his very valuable article, "Nerves of Muscles and Tendons," "Schäfer's Text Book of Physiology," vol. ii., gives a very complete account of the subject of muscle spindles and end organs, together with a

¹ "In the skeletal muscles there are, as we have seen, three sets of sensory organs, *e.g.*, muscle spindles, tendon organs, Pacini corpuscles, modified and typical."

PLATE VII.

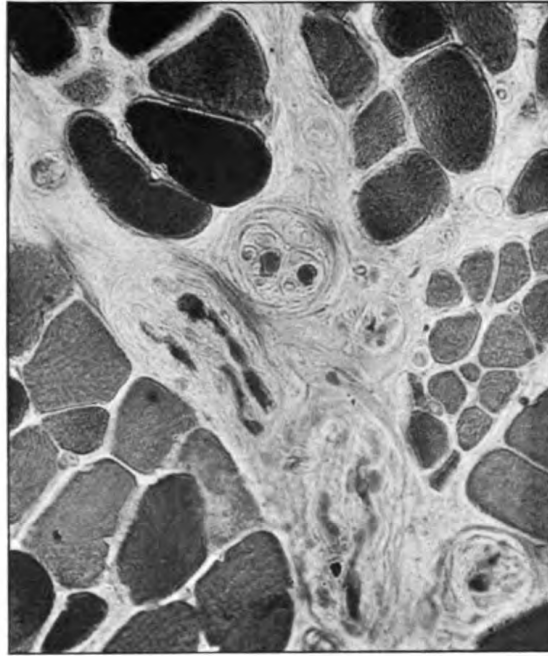


FIG. 1.

Photomicrograph of a group of spindles in hallux muscle. Weigert stained nerve fibres in longitudinal section are seen, and two in transverse section of a spindle. Magnification 350.

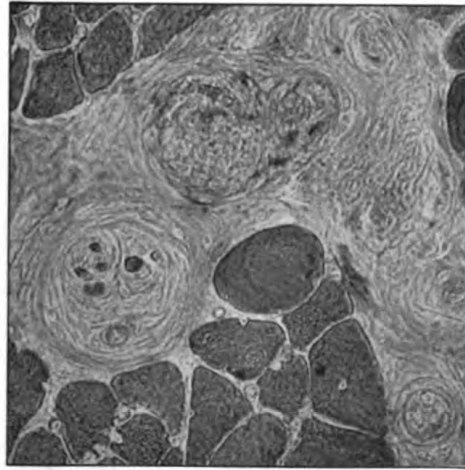


FIG. 2.

Photomicrograph of a section of the hallux muscle, Weigert stained. The lower one shows nerve fibres in transection and is fairly normal. The upper is degenerated. There were comparatively to normal hallux muscles very few spindles to be found with normal appearances. Magnification 350.

complete bibliography, to which I will refer the reader for further information on this interesting subject.

This disease, then, is characterised by a failure of the neural systems, which transmit, receive, coördinate and execute voluntary movements. The only system which is not eventually affected is the spinal motor efferent, which innervates muscle (*vide* diagram, p. 200).

But the muscular sense or kinæsthesia is a complexus of impressions arriving from different nerve endings, each one structurally adapted to fulfil a special purpose. The spindle may be stimulated by the active current of the muscle in contraction, and thus when the intrafusal muscle contracts the annular nerve spiral wrapped round its equatorial portion would be stretched and excited. Again, when the muscle is stretched and the intrafusal fibres by virtue of their elasticity are extended, the annular nerve spiral would be stimulated, but in a different manner. The form of the Pacinian corpuscle would suggest that it is especially adapted for stimulation by compression, and those Pacinian corpuscles which are situated in the septa of sheaths and aponeurosis of muscle would be particularly sensitive to every alteration in contraction and extension of the muscle fibres. It is possible that the Pacinian corpuscles contained in muscle are continually transmitting impulses while it is in a state of tonic contraction; whereas the spindles, as said before, excited by action currents, signal only active states, therefore the nerves of the former may transmit impulses to the cerebellum, and the nerves of the latter transmit impulses by the long tracts of the posterior columns to the post-central convolutions. Sense organs of joints certainly contribute in no small degree to the various kinds of muscular sense impressions. The skin does not assist much in muscular sense. In tabes, joint sensations are lost later than those of the muscular sense.

There are, therefore, physiological, clinical and anatomical reasons for believing that this disease is a neuronie abiotrophy, affecting the whole kinæsthetic systems of neurons from periphery to centre, and that in consequence

of the absence of stimulus in the cortical sensory receiving station, there results a secondary degeneration of (the Betz cells) psycho-motor neurons. Where does this process of atrophy start? All cases show degenerative atrophy of the posterior columns and cerebellar tracts, but a considerable number show no degeneration or only comparatively slight degeneration of the crossed pyramidal tracts. All cases have not shown degeneration of the peripheral nerves. It is probable, therefore, that the disease commences by an atrophy of the intraspinal terminals of the kinæsthetic proto-neurons, then of the posterior roots and the peripheral nerves, and lastly of the cells of the posterior spinal ganglion. The neurons, consisting of small cells and fine fibres which subserve cutaneous sensory and viscerovascular functions, are in great part, if not entirely, spared. At least we may presume that this is true, for we find, as others before have found, that the fine fibres escape, and that, unlike tabes, there is little or no affection of cutaneous sensibility and no visceral disturbances. In Friedreich's disease, even in such an advanced case as this, the fine fibres appear to be intact in the posterior roots, whereas I have shown in the examination of a large number of cases of tabes, that there is a correlation of visceral crises and cutaneous sensory disturbances, with absence of fine fibres in the posterior roots, and sclerosis of Lissauer's tract.¹ Reference to the subjoined literature on this subject supports the above statements.

A CASE OF FRIEDREICH'S HEREDITARY ATAXIA WITH NECROPSY, BY
GEORGE E. RENNIE, *British Medical Journal*, JULY 15, 1899.

The case is of interest on account of the short duration of symptoms—fifteen months.

Degeneration of the posterior roots, of the posterior root zones, and of the posterior columns, *less defined degeneration of the crossed pyramidal system*. Distinct degeneration of the cerebellar tracts, and atrophy of the cells of Clarke's columns.

These findings correspond pretty closely with those previously recorded, and are generally recognised as the typical lesions of

¹ "Tabes in Hospital and Asylum Practice."—"Archives of Neurology." vol. ii.

Friedreich's ataxia. "It is of interest to note how well-defined the lesions were, though the duration of the disease was stated to be only about fifteen months, while in all the other recorded cases with necropsies the disease had lasted years." This case seems, therefore, to show that the disease is a primary abiotrophy of the kinæsthetic sensory neuron.

In only a few instances of necropsies on Friedreich's disease have the peripheral nerves been examined. In some of these the nerves are reported to be normal, in others degenerated, but in all the posterior roots have been found much atrophied. It would appear, therefore, probable that in this case the peripheral nerves had not degenerated. As in *tabes dorsalis*, it is extremely likely that the intraspinal projections of the sensory proto-neurons are the first to suffer. Rennie does not appear, however, to have examined systematically the peripheral nerves in this case.

Mackay records a careful examination of the peripheral nerves in a case of Friedreich's disease, and I will allude somewhat fully to his interesting researches.

He also gives a summary of autopsies on eighteen certain cases and four doubtful cases, as well as a bibliography of the subject up to date. He remarks upon the absence of coarse fibres in the posterior roots and the presence of large numbers of fine fibres; the probable existence of pigmentary degeneration of the posterior spinal ganglion cells is noted, also the increase of endo-neuron between the nerve fibres and interstitial connective tissue nuclei between the ganglion cells.

The anterior roots showed abundant large nerve fibres 10 to 12 μ , and contrasted strongly with the posterior roots.

The degenerative atrophy of the fibres in the peripheral nerves is described and connective tissue hyperplasia noted.

He remarks that none of the pathological changes described are new to the literature of the disease. "In many features the case bears a close resemblance to some of the more recently reported cases, those of Simon, Bonners, Merto, and Guizetti. Lissauer's tract was more or less affected in each, as it was also in two other cases."

The peripheral nerves were atrophied or degenerated in a number of cases, and in some it has reached an extreme degree.

The nature of the fine fibres observed in the peripheral nerves and posterior roots in this, as in other cases of Friedreich's disease, is of great interest when taken in conjunction with the fact that Lissauer's tract suffers little, if at all, in comparison with the other sensory fibre systems.

Auscher, Guizetti, Mackay, and Tedeschi refer to the various conditions found existing in the fine fibres.

He discusses the vascular origin of the disease, and remarks that in his case the vessels and capillaries were nowhere markedly

thickened, but were everywhere distended with blood cells. The last-mentioned fact is of interest in relation to the vascular theory of the causation of the disease which was favoured by Pitt, Blocq, and Marinesco. These observers found changes in the blood-vessels of the posterior columns, as also did Schultze in his second case, and Everett Smith. On the other hand, no changes were described by Rutimeyer, Dejerine and Letulle, Guizetti and Mackay.

He agrees with Guizetti that the disease depends upon a congenital predisposition, in consequence of which in the early years of life, certain systems of fibres and nerve cells undergo a process of progressive atrophy, and the process is independent of any contributory effect from vascular alterations.

He excludes from his list all cases of cerebellar type of the disease, with which Nonne, Menzel, Marie, Sanger Brown, and others have made us familiar.¹

Llewellys Barker has recently made a very exhaustive and careful investigation of the central nervous system of one of Dr. Sanger Brown's American family of hereditary ataxia. He states: "The present report, together with that of Dr. Adolf Meyer's report on another case belonging to this family makes it clear that the morbid anatomy of the affected members of the family described by Dr. Sanger Brown, presents very constant features; we now know with certainty the neuron systems principally involved in the individuals who are affected, though we are as yet entirely ignorant as to why just these neuron systems should be picked out.

"In this case the symptoms did not commence until the patient was 20 years of age. There was marked degeneration in the nerve cells and nerve fibres of centripetal paths including one system of exogenous fibres of the posterior funiculus, the nucleus of Clarke and the direct cerebellar tract. There was some involvement of the dentate nucleus of the cerebellum. The crossed pyramidal tracts apparently were not affected and there was no change in the cerebral cortex noted. The peripheral nerves and muscles and the spinal ganglia are not described. A very careful description of the cerebral topography is given of two cases and the resemblances and differences observed in the brains of two brothers are noted."

Correlation of the Clinical Symptoms with the Morbid Changes.—

The first and essential clinical symptom of Friedreich's disease is a disturbance of coördination of the lower, and later of the upper extremities. There is both locomotor and static ataxy. The gait is a combination of the tabic and cerebellar type of ataxy. There is, moreover, a characteristic unrest of the muscles, reminding one of chorea minor. Nystagmus and speech disturbance follow and are important symptoms. The deep reflexes are

¹ "Pathology of a Case of Friedreich's Disease." Mackay, *Brain*, 1899.

abolished. The Argyll-Robertson pupil is absent. Cutaneous sensory disturbances are rare and only occur in the latest stages of the disease. Lancinating pains are exceptional, visceral crises are absent and bladder disturbances are, as a rule, not met with. In the last stages of the disease paresis and paralysis are met with. An early appearance of paralysis does not occur. Scoliosis is very frequently met with, also a kyphosis. Deformities of the extremities usually occur in the later stages, especially club foot, talipes varus-equinus and equino-varus and pes cavus.

The disease usually lasts twenty to thirty years, and even longer, and death arises from intercurrent disease and complications. Such is the classical description of a case of Friedreich's disease. It must, therefore, by analogy with other cases, even in the absence of any history of heredity, be supposed that this degenerative atrophy was the result of an inborn defect and be considered as a case of Friedreich's disease. Moreover, the fact that the central canal of the spinal cord showed throughout a peri-epindymal glia overgrowth and that there was evidence in the lumbo-sacral region of only a partial closing up of the primary embryonic medullary canal and formation thereby of the posterior median fissure suggests a primary inborn defect of those neurons the fibres of which grow into the posterior columns and press together the two sides of the canal. These fibres are mostly the larger fibres which are contained in the posterior roots and transmit kinæsthetic impulses. The fact that a failure of coördination of the lower limbs is the first evidence of the disease would indicate that the process of abiotrophy commences primarily in the sensory proto-neurons. Seeing that the knee jerks are absent from the first and there is no disturbance of the cutaneous sensibility it may be supposed that the disease affects primarily those sensory neurons whose intraspinal projections form (1) the root zone, and terminate by arborisation with intercalary cells at the base of the posterior horn, forming thus the principal sensory portion of the reflex arc and especially related to the maintenance of reflex spinal tonus. (2) The coarse fibres which end in a brushwork around the cells of Clarke's column, forming the first system in the afferent channel to the cerebellum, probably this is rapidly followed by and perhaps associated with atrophy of the cells of Clarke's column and the ventral and direct cerebellar tracts. (3) Atrophy of Goll's column, the first system in the cerebral tract (*vide* diagram).

In cases where there is early a cerebellar as well as spinal ataxy, we must presume there is a lesion of the corpus dentatum. Probably, for reasons already stated, the Betz cells and the pyramidal system are affected later.

This case is of interest in supporting the neuron doctrine, for

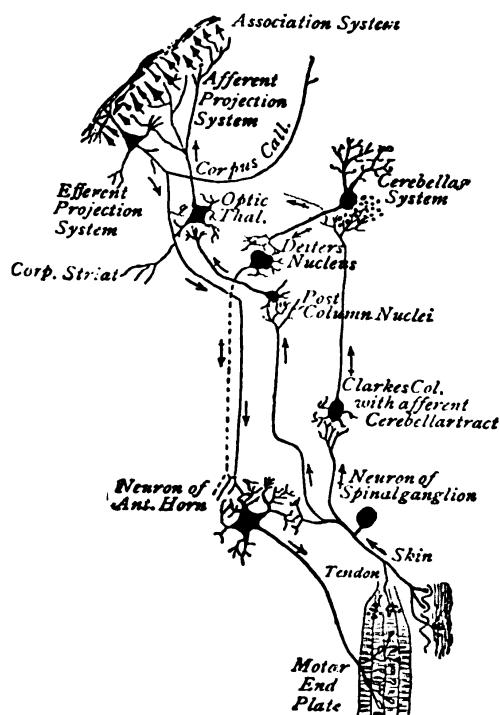


Diagram representing the systems of neurons which are in action in all voluntary movements. It will be observed that three reflex circles are represented—spinal, cerebellar, and cerebral. All the systems of neurons are affected in this case, except the spinal efferent neurons directly innervating the muscles, and the sensory skin neurons.

we find systems and communities of neurons physiologically correlated by functional association, but anatomically widely separated, undergoing insidious progressive and systemic decay which is selective in its operation and cannot be explained upon anatomical or mechanical constricting influences, such as have been, in my opinion, erroneously put forward to explain tabes. The only explanation which well fits the facts is an inborn defect in the specific energy of the kinæsthetic neurons. It might be urged that this in no way proves the neuron doctrine, for there is a fibrillary continuance wherever there is physiological correlation. If this were so then the fillet should atrophy and there should be as complete a disappearance of the internal arciform fibres as there is disappearance of the Betz cells.

BIBLIOGRAPHY.

- SHERINGTON. "Text-Book of Physiology," Schäfer.
- FRIEDREICH. "Ueber Ataxie mit besonderer Berücksichtigung der hereditären Formen," *Virchow's Archiv*, p. 68.
- MEYER. "The Morbid Anatomy of a Case of Hereditary Ataxy," *Brain*, 1897, p. 276.
- BRAMWELL. "Remarks on Friedreich's Ataxy, with notes of three cases," *Brit. Med. Journal*, 1897, vol. ii., p. 896.
- MACKAY. "Pathology of a Case of Friedreich's Disease," *Brain*, 1898.
- MARIE, O. "Sur l'hérédité Ataxia Cérébelleuse," *Semaine Medicale*, 1893.
- MUERA. "Ueber l'hérédité Ataxie," *Mittheilungen der Med. Fakultät d. k. Japan Univers.* Tokio, iv. 1898.
- RENNIE. "A Case of Friedreich's Hereditary Ataxy, with Necropsy." *Brit. Med. Journal*, 1899, 15, vii., p. 129.
- SPILLER. "Four Cases of Cerebellar Disease (one autopsy), with reference to cerebellar hereditary ataxia," *Brain*, 1896.
- SCHMAUS AND SACKI. "Pathologische Anatomie des Rückenmarke."
- WHYTE. "Four Cases of Friedreich's Ataxia," *Brain*, 1898.
- BARKER, L. "Description of Brain and Spinal Cord in Hereditary Ataxia." Decennial Publications, University of Chicago.

NOTES ON THE WEIGHT AND THE CONVOLUTIONAL PATTERN IN SEVEN CHINESE BRAINS.

By P. HARPER.

(*Student, St. Thomas's Hospital.*)

THE following account is a summary of the results of an investigation of seven Chinese brains kindly placed at my disposal by Dr. F. W. Mott, the director of the Pathological Laboratory at Claybury. The work was done during the months of June and July, 1906, at the laboratory. A full description of these brains was written, but in consultation with Dr. Mott and Mr. Parsons, it was decided to publish only a summary of these observations. I wish to express my indebtedness to Dr. Mott and Mr. Parsons for their advice and help in this investigation.

The seven specimens were as follows: five brains of Chinamen sent from the Straits Settlement by Dr. Fry, the brain of a Chinese coolie, of good physique and stature, who died of beri-beri at the Seamen's Hospital, and the brain of a Chinaman sent from Singapore; the last two brains had been preserved in alcohol. The following is a brief *resumé* of the notes accompanying the brain sent by Dr. Fry.

It will be observed that several different Chinese nationalities are represented, and it is probable that this may have something to do with the differences in the convolutional pattern and weight of the brains. It is unfortunate that there is no note regarding the stature, physique and body weight, which, of course, would influence considerably the weight of the brain.

Specimen II.—Male, Chinese, aged 25. Died of exhaustion due to dysentery.

Specimen III.—Male, Chinese (Nationality Hylam), aged 40. Died of syncope due to pneumonia.

Specimen IV.—Male, Chinese (Nationality Hylam), aged 30. Died of dysentery.

Specimen V.—Male, Chinese (Nationality Macao), aged 29. Died from pulmonary tuberculosis of both lungs.

Specimen VI.—Male, Chinese, aged about 40. Died of plague.

The five brains obtained from Dr. Fry were preserved in formalin. The apparent weights obtained by weighing these specimens, when the excess of formalin had been allowed to run off, have been multiplied by $\frac{10}{11}$, since brains preserved in formalin gain 10 per cent. of their weight.

The left hemisphere and the brain from Singapore were preserved in alcohol. Since brains preserved in alcohol lose 30 per cent. of their weight, the apparent weights of these specimens, when the excess of alcohol had been allowed to run off, was multiplied by $\frac{10}{7}$ to obtain the real weights.

It is then seen that

I. (α) Only two out of these six male Chinese brains weighed as much as the average male European brain, which is 1360 grammes. Of these, No. II. weighed 1370 grammes, and No. VI. weighed decidedly over 1367 grammes. But no deductions can be drawn from this, since the height and total body weight of the men from whom the brains came is not known.

(β) Since the sum of the weights of the whole unstripped brains Nos. II., III., IV., and that from Singapore is 5226·35 grammes, or an average weight per brain of 1306·58 grammes, whilst the sum of the real weights of the unstripped cerebella of these four brains is 629·46 grammes, or an average of 157·36 grammes, it follows that in these four brains the average weight of the cerebellum is less than $\frac{1}{8}$ of the average weight of the whole brain.

Taking each of these four brains separately, in No. II. the cerebellum is slightly more than $\frac{1}{8}$ of the weight of the whole brain; in No. III. it is a great deal less than $\frac{1}{8}$ of the weight of the whole brain; in No. IV. it is a little greater than $\frac{1}{8}$ of the whole brain, whilst in the brain from Singapore it is a little less.

With regard to the remaining two brains, No. V. was not weighed unstripped, but the real weight of the stripped cerebellum (149 grammes), is less than $\frac{1}{8}$ of the weight of the whole stripped brain (1260·9 grammes).

Brain VI. must have been the heaviest of all, since though the medulla and half of the cerebellum and pons had been cut away before packing, its real weight was still 1367 grammes.

Thus in three out of five of these Chinese brains the cerebellum is less in weight than $\frac{1}{8}$ of that of the whole brain. In other words, this small number of cases shows that the cerebral part of the brain is slightly larger in proportion to the cerebellar than it is among Europeans.

The larger size of the cerebrum is due to a very large frontal lobe.

(γ) The average weight of the right hemisphere differs only by ·44 gramme from that of the left.

Brain.	Right Hemisphere.	Left Hemisphere.	Difference.
II.	571·8 grms.	580·9 grms.	L. 9·1
III.	556·36 „	563·63 „	L. 7·29
IV.	513·63 „	495·45 „	R. 18·18
V.	549·09 „	562·72 „	L. 13·63
VI.	653·63 „	647·27 „	R. 6·37
Brain from) Singapore)	567·14 „	564·28 „	R. 2·86
Total	3411·65 grms.	3414·25 grms.	L. 2·61
Average	568·60 „	569·04 „	·4

It will be seen that in three out of six cases the right hemisphere was heavier than the left. The greatest pains were taken to divide the organ symmetrically.

SUMMARY (II.)

(2) *Fissure of Sylvius.* (a) *Sylvian angle.* The greatest angle made by the fissure of Sylvius with the horizontal plane in those cases in which the direction of the fissure is not altered by artificial pressure is in brain No. VI., in which the angle is 20° on each side. In No. V., on both sides, there is practically no angle, the fissure being almost parallel to the horizontal plane, and in the left hemisphere of the brain from Singapore the fissure is also almost parallel to the horizontal plane. In Specimen A, the left

hemisphere of another Chinese brain, the Sylvian angle is minus, that is to say, it would not cut the horizontal plane anteriorly, however far it was produced, but would cut it if produced backward, since the fissure runs from in front backward and downward. See fig. 1 (s.).

The angles made by the remaining fissures of Sylvius with the horizontal plane could not be relied upon, as, in all these cases, the fissures had suffered from the effects of artificial pressure.

The tendency of the Sylvian fissure in these brains to become horizontal is due to the great frontal development, and consequent shifting backwards, of the Rolandic fissure, and prefrontal gyrus, which is the deepest part of the frontal lobe.

II. (β) One of the most constant features of the Sylvian fissure in these brains is the continuation of the posterior horizontal limb backward past the point at which its upturned extremity runs up to be surrounded by the supra-marginal gyrus. See fig. 1 (b) fig. 3 (b). In only three hemispheres is there no indication of this backward continuation of the posterior horizontal limb. These are the left hemisphere of the brain from Singapore, the right hemisphere of No. II., and the left hemisphere of No. III. Of the last-named, however, the posterior horizontal limb is peculiar. It is 6.75 cm. long, and has practically no upturned posterior extremity, this being represented by the posterior 5 mm. of the fissure, which has a very slight inclination upwards.

In the remaining ten hemispheres, the backward continuation is well-marked. It varies in length from a few mm. to 2.25 cm. Its most usual direction is backward and downward, so that it points towards the occipital pole. In one case (the right hemisphere of the brain from Singapore) the posterior horizontal limb is continued backward for 5 mm. past the posterior upturned extremity, and then bifurcates into an upper limb, 2 cm. long, and a lower limb, 1.5 cm. long.

With regard to the anterior limbs of the Sylvian fissure, in only one case (the right hemisphere of No. IV.) do the two limbs come off from the stem of the Sylvian fissure

by a common trunk. This trunk runs up for 5 mm., and then divides into a short anterior ascending limb and an anterior horizontal limb, which is 2 cm. long.¹ On the left side of No. IV. the anterior limbs are peculiar. Here the ascending limb ends on reaching the lateral surface, whilst the horizontal limb runs forward and upward for 1.2 cm. and then bifurcates into an anterior and posterior branch, each of which is 1 cm. in length.

In five of the hemispheres there is a well-marked sulcus retro-centralis transversus. These are the left hemispheres of Nos. VI., II., III. and IV., and the right hemispheres of No. II.

The only hemispheres in which there is a well-marked sulcus præcentralis transversus are the left hemispheres of Nos. II., V. and VI.

III. In every case the frontal lobe is large, both actually and relatively to the rest of the hemisphere. This is due chiefly to the great development of the inferior and middle lobules. The superior lobule is in almost every case narrow, but, as is shown by the fact that the upper end of the Rolandic fissure is always more than 2 cm. behind the mid-point of the supero-mesial border, the superior lobule is always somewhat long. The convolutional pattern of the superior lobule is in all cases simple. There are usually several sulci paramesiales. The superior frontal sulcus usually runs a straight course forward and slightly inward, and so does not add to the complexity of the convolutional pattern of the superior lobule.

The middle lobule is in all cases large and divided up by secondary fissures. In only one case, the left hemisphere of No. IV., does a long horizontal middle sulcus run forward through the whole length of the lobule. In all other cases the lobule is marked by vertical or oblique sulci in its posterior three-fifths.

The inferior lobule is in every case large. It is deeper transversely and shorter antero-posteriorly than either the superior or middle lobules. In every case it is larger (that is, deeper) on the left than on the right side.

¹ This arrangement is recorded by Cunningham as occurring in 32 per cent. of European brains.

The relative sizes of the partes basilaris, triangularis and orbitalis vary. In seven cases the pars basilaris is of average or more than average size. In these cases it is marked by one or more fissures.

In every case the pars triangularis is the largest subdivision of the inferior lobule. A very constant feature of this part is a downward branch of the inferior frontal sulcus. In only three cases is this branch absent, and in one of these cases the pars triangularis is fissured by a very deep sulcus, which is only prevented by a deep gyrus from being confluent with the inferior frontal sulcus. In each of the other two cases, the surface of the pars triangularis is enfolded by a fissure which in one case is isolated, whereas in the other it is confluent below with the Sylvian.

In eight cases the downward branch of the inferior frontal sulcus is the outer limb of the bifurcation of that fissure. In two of these cases, as well as the outer limb of its bifurcation, another downward branch of the inferior frontal sulcus also cuts into the pars triangularis. See fig. 3 (*d*). In many cases the pars triangularis is also marked by isolated fissures.

This downward branch of the inferior frontal sulcus is probably formed first as an isolated fissure by the expansion and consequent infolding of the cortex of this region. This stage is seen in two of the cases described above. As the cortex goes on expanding, it is correspondingly more infolded, and the fissure grows until it becomes confluent above with the inferior frontal sulcus, as in the majority of the cases, and perhaps below with the Sylvian fissure, as in one case.

In only seven out of the thirteen cases, Nos. V. R., VI. R., VI. L., IV. R., IV. L., and R. and L. of brain from Singapore, can the pars orbitalis be said to exist at all, and in two of these it is extremely small (Nos. V. R. and VI. R.). In one case, No. IV. R., it is almost as large as the pars triangularis. In one case its surface is infolded by the outer limb of the bifurcation of the inferior frontal sulcus (No. VI. L.), and in another case by an isolated fissure (the left hemisphere of the brain from Singapore).

In two cases the ascending frontal lobule is divided into two parts by the lower part of the superior præcentral sulcus which turns back to meet the Rolandic fissure. In one of these cases, the left hemisphere of the brain from Singapore, the two parts are connected by a deep gyrus. In the other case, the left hemisphere of No. II., the two parts are completely separated from one another.

In one brain there is a single præcentral sulcus. This is the right hemisphere of the brain from Singapore. In eleven of the remaining twelve cases the superior and inferior præcentral sulci are separated by a superficial gyrus, and in the one other case a deep gyrus separates the two sulci.

In every specimen the superior frontal sulcus is confluent with the superior præcentral or, in the case mentioned above, with the single præcentral sulcus.

In ten hemispheres, the inferior frontal sulcus starts from the inferior præcentral. In two cases, the right hemisphere of No. II. and the left hemisphere of the brain from Singapore, the inferior frontal and inferior præcentral sulci are separated by superficial gyri. In the right hemisphere of the brain from Singapore, the inferior frontal sulcus is separated from the single præcentral sulcus by a superficial gyrus.

IV. *Rolandic fissure*.—In seven out of these thirteen hemispheres the Rolandic fissure is continued above on to the mesial surface for distances varying between a few millimetres and 1.75 cm. These are Nos. VI. L., III. R., III. L., IV. R., IV. L., and R. and L. of brain from Singapore.

In every case the upper extremity of the Rolandic fissure (or in those cases in which it is continued on to the mesial surface, the point at which it crosses the supero-mesial border) is placed *at least* 2 cms. behind the mid-point of the supero-mesial border. In the right hemisphere of No. VI., the upper end of the Rolandic fissure is 4 cm. behind the mid-point of the supero-mesial border. The increase in size of the frontal lobe, which might be expected to follow from the above condition, is to a certain extent negated by the smallness of the Rolandic angle, which

averages 59.4° for these brains, instead of 71° as in the normal European brain.

In three cases only does the Rolandic fissure appear to be confluent with the Sylvian. In two of these cases, the right hemispheres of Nos. V. and IV., the apparent connection is established by means of a small fissure continuing downwards the course of the Rolandic fissure, but separated from it by a deep gyrus. In the right hemisphere of No. V. this small fissure is separated from the Sylvian by a deep gyrus.

In the third case, the left hemisphere of the brain from Singapore, the Rolandic fissure is crossed at its junction with the Sylvian by a deep gyrus.

In every case at least one buttress of cortex projects into the fissure from its posterior lip.

SUMMARY V.

Parietal lobe.—In both hemispheres of brain No. III., the parietal lobe is of average size relatively to the rest of the hemisphere. *In every other case the parietal lobe is relatively small.* This is due chiefly to the large size of the frontal lobe, which, as it were, pushes back the parietal so that the latter is small antero-posteriorly rather than vertically. As might be expected from this, there can be found no constant diminution of any one lobule relative to the whole lobe.

In the right hemispheres of No. II. and of the brain from Singapore the supramarginal gyrus is not separated in front from the ascending parietal lobule. In other cases the supramarginal gyrus is well developed and distinct. The angular gyrus is large except in No. V., where it is small. See fig. 3 (a). The occipital annectant is less constant than the parietal or supra-marginal annectants, and in four cases is blended with the postparietal gyrus.

SUMMARY VI.

Calcarine fissure.—The anterior calcarine fissure varies in length from less than 1.9 cm. in the left hemisphere of No. V., to 4.5 cm. in the right hemisphere of No. VI.

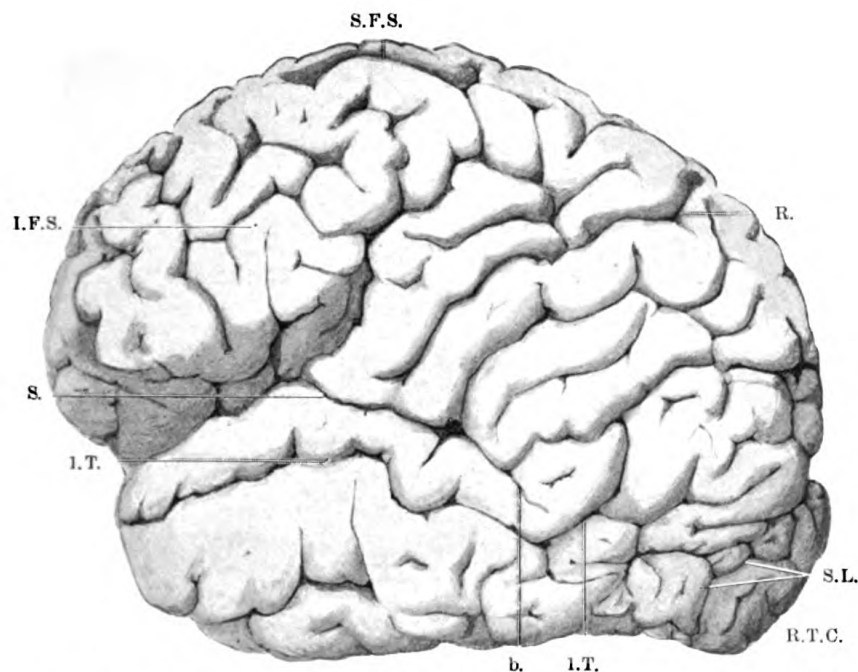


FIG. 1.—Outer surface of the left hemisphere of a Chinese brain (referred to in the text as A).

S.—Sylvian fissure.
R.—Rolandic fissure.
S.L.—Sulcus lunatus.

I.T.—First temporal sulcus.
b.—Backward continuation of Sylvian fissure.

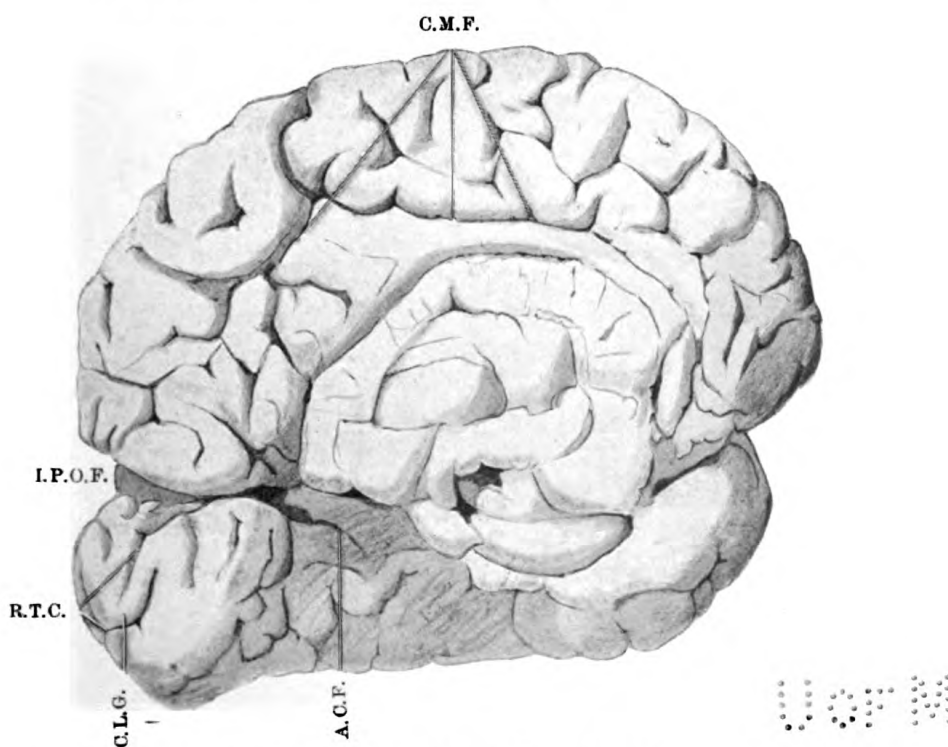


FIG. 2.—Mesial surface of hemisphere A.

I.P.O.F.—Internal parieto-occipital fossa.
R.T.C.—Retro-calcarine fissure.
C.L.G.—Superficial cuneolingual gyrus.

A.C.F.—Anterior calcarine fissure.
C.M.F.—Calloso-marginal fissure.

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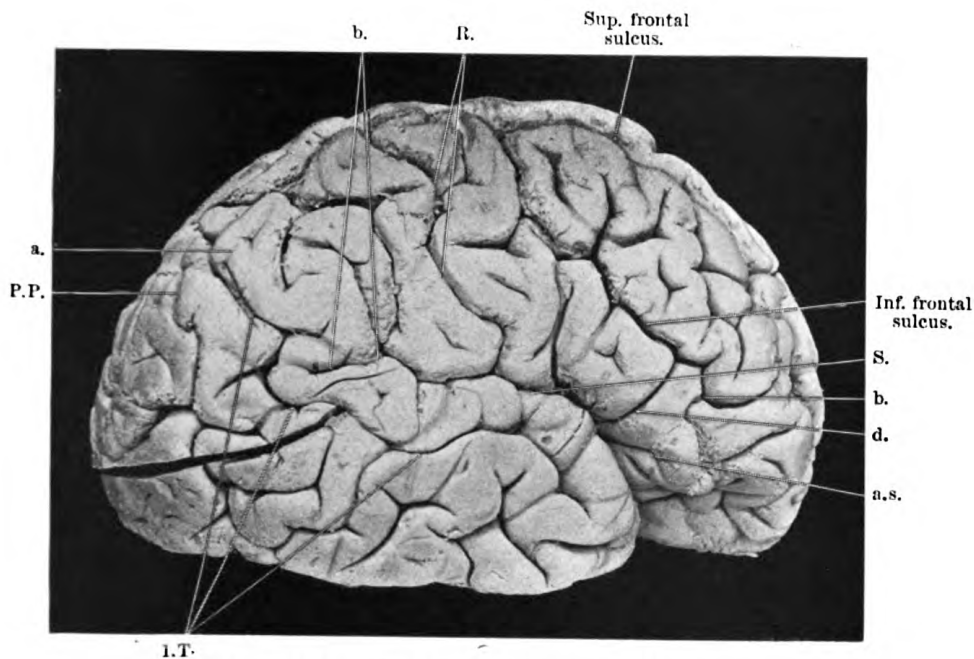


FIG. 3.—Outer surface of right hemisphere of brain No. V.

S.—Sylvian fissure.
R.—Rolandic fissure.
I.T.—First temporal sulcus.
a.s.—Anterior horizontal limb of Sylvian fissure.
b.—Backward continuation of Sylvian fissure.

d.—Downward branch of inferior frontal sulcus, cutting into the pars triangularis.
b.—Bifurcation of inferior frontal sulcus.
a.—Angular gyrus.
P.P.—Post parietal gyrus.

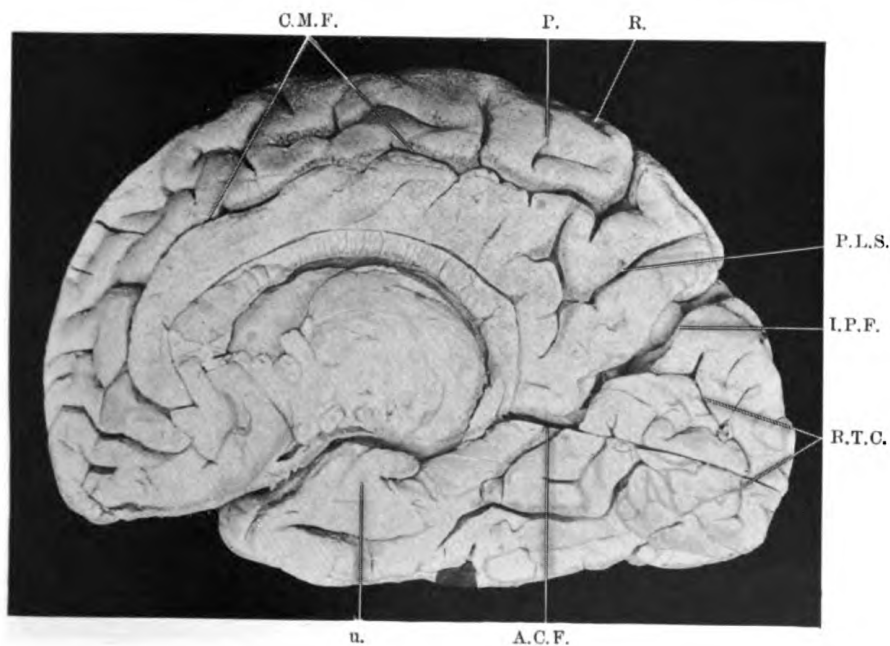


FIG. 4.—Mesial surface of right hemisphere of Chinese brain No. V.

A.C.F.—Anterior calcarine fissure.
R.T.C.—Retro-calcarine fissure.
I.P.F.—Internal parieto-occipital fossa.
P.L.S.—Postlimbic fissure.

C.M.F.—Calloso-marginal fissure.
R.—Upper extremity of Rolandic fissure.
P.—Paracentral convolution.

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In one brain, that from Singapore, it is longer on the left than on the right side. In the five other brains it is longer on the right side.

On the right side of No. II. the anterior calcarine fissure is confluent with the collateral.

In eight cases the retro-calcarine fissure extends on to the outer surface of the occipital lobe. These are tabulated below, giving the number and side (whether R. or L.) of the hemisphere, and the extent of the fissure backward.

A. (L.) ends on outer surface of occipital lobe in posterior lip of sulcus lunatus. See figs. 1 and 2 (R.T.C.).

VI. (L.) extends on outer surface for 3.5 cm., and ends in posterior lip of sulcus lunatus.

II. (R.) extends on outer surface for 2 cm., ends in concavity of V-shaped sup. occ. sulcus placed on posterior lip of sulcus lunatus; II. (L.) same as II. (R.)

III. (R.) ends on outer surface of occipital pole in vertical fissure of Seitz. S. lunatus is 2 cm. in front of occ. pole. (L.) extends on outer surface for 2.2 cm., and ends just behind vertical sup. occ. sulcus placed on the posterior lip of the sulcus lunatus.

IV. (R.) extends on outer surface for 1 cm. and ends just behind a <-shaped superior occipital sulcus placed in the posterior lip of the sulcus lunatus.

Singapore brain (R.) extends on outer surface of occipital lobe for 4 mm. from the pole.

In two hemispheres, V. L. and IV. L., the retrocalcarine fissure had been cut away.

In V. R., it ended in a descending fissure on the mesial surface. See fig. 4 (R.T.C.).

In VI. R., it ended on the mesial aspect of the pole in a descending fissure, of which the inferior extremity turns over the infero-mesial border.

In the left hemisphere of the brain from Singapore the fissure is altogether peculiar. It runs back from the internal parieto-occipital fissure for 1.5 cm. and then ends in the middle of a vertical fissure 3.5 cm. long, thus forming a $\neg$. Behind this there is a superficial cuneo-lingual gyrus, bounded posteriorly by another vertical part of the intra-

striate fissure, parallel to the former and 4 cm. in length and running from the supero-mesial to the infero-mesial border.

In these brains any difference in size between the right and left parietal lobes, if it exists at all, is not very evident.

In two brains, Nos. VI. and III., the retro-calcarine fissure of the left side extends on to the outer surface of the occipital lobe for a greater distance than does the retro-calcarine fissure of the right side.

In one case there is no difference on the two sides, and in one case (the brain from Singapore), the retro-calcarine fissure of the left side is peculiar, and does not reach the outer surface, whilst on the right side it is continued on to the outer surface for 4 mm.

In the remaining cases parts of the occipital lobes had been removed, so that the retro-calcarine fissure could not be studied.

Line of Gennari.

As in the case of the retro-calcarine fissure, the line of Gennari would be expected to come further forwards on the outer surface of the left lobe than of the right. If the striate area be of equal extent on the two sides, and if it comes forward on the outer surface of the left occipital lobe for a greater distance than on that of the right lobe, a larger part of the striate area will be expected on the mesial surface of the right side than of the left. That is to say, the line of Gennari would be expected to extend on the right side either further forward into the ventral lip of the anterior calcarine fissure or higher into the cuneus, or lower into the lingual convolution, than on the left side.

Taking first the extent to which the line of Gennari is continued posteriorly on to the outer surface of the occipital lobe, of six cases, in one the extent is equal on both sides. This is brain No. II.

In one case (the brain from Singapore) the striate area extends 2 mm. further forwards from the pole on the outer surface of the occipital lobe on the right side than

on the left. In the remaining four cases, the striate area is prolonged further forward on the outer surface of the left lobe than of the right. This is what would have been expected. These four cases are tabulated below, with the distance to which the striate area extends forward on the outer surface of the occipital lobe measured from the pole.

Extension forwards of striate area on outer surface of occipital lobe.

Brain.	Right Side.	Left Side.
V.	Nearly 1 cm.	1 cm.
VI.	0	2.5 cm.
III.	5 mm.	2.5 cm.
IV.	2 cm.	3.8 cm.

It would be expected, then, that in these four brains the striate area would extend on the right side, either further along the ventral lip of the anterior calcarine fissure than on the left side, or higher into the cuneus, or lower into the lingual convolution. That it does not constantly extend further into the ventral lip of the anterior calcarine fissure on the right side than on the left side is shown by the following table :—

Measurement of extension of area striata into ventral lip of anterior calcarine fissure.

Brain.	Right Side.	Left Side.
V.	0	1.8 mm. (whole length of fissure)
VI.	2.25 cm. (half-way along fissure)	3.5 cm. " " "
III.	1.5 cm. " " "	1.4 cm. (more than half-way).
IV.	1 cm. (one-third of way along fissure)	0

Thus, of these four brains, in which the striate area extends further forward on the outer surface on the left side than on the right side, in two cases it extends also further forward on the left side than on the right.

In one (No. IV.) it extends further forward on the right side, and in the remaining case (No. III.) its extension anteriorly is only 1 mm. more on the right than on the left side, so that it may be looked upon as the same anteriorly on the two sides.

In the brain from Singapore, in which the striate area extends 2 mm. further forward on the outer surface of the occipital lobe on the right side than on the left side, it extends into the ventral lip of the anterior calcarine fissure of the left side 2.2 cm., whereas on the right side it only does so for 5 mm.

In No. II., in which the striate area extends for an equal distance (3.5 cm.) from the pole on the outer surface of the occipital lobe, it extends into the ventral lip of the anterior calcarine fissure of the left side for 1.5 cm., whilst on the right side it does not extend into the ventral lip of the anterior calcarine fissure at all. In these cases in which the striate area extends further on the left side than on the right, both backwards round the occipital pole, and forwards into the ventral lip of the anterior calcarine fissure, the total striate area may yet be equal on the two sides if it extends higher or lower on the right side than on the left. In No. III. the area does extend much further downwards into the lingual lobule on the right side than on the left side. But this side of the question is further complicated by the depth of the intra-striate fissures, since a deeper fissure will infold more striate area than a shallower one.

Dr. Mott has also pointed out that the extent of the striate area is the same on the two sides, and that when it extends on to the external surface the cuneo-lingual annectents which lie at the bottom of a shallow calcarine fissure are small relatively. The extension of a few mm. on the lower lip of the anterior calcarine fissure would not materially affect the superficies of the striate area.

SUMMARY VII.

The external parieto-occipital fissure.—Elliott-Smith has shewn that the external parieto-occipital fossa is formed in the brains of Egyptians by the continuation on to the outer surface of one or more of the three fissures found in the internal parieto-occipital fossa. This is found also to be the case in these Chinese brains.

Of these three fissures the middle one is called the incisura parieto-occipitalis, and is bounded in front, below, and behind by a U-shaped gyrus, which is continuous above with the gyrus arcuatus, and is named the arcus intercuneatus. The incisura is present in the upper part only of the internal parieto-occipital fossa, where it is vertical in direction, and, with the arcus intercuneatus, lies deeply, so that the lips of the fossa have to be pulled

apart to expose it. In its fully developed condition, it is continued above over the supero-mesial border, from which it is directed transversely outwards to form the external parieto-occipital fissure, and is bounded externally by the arcuate gyrus. See fig. 5.

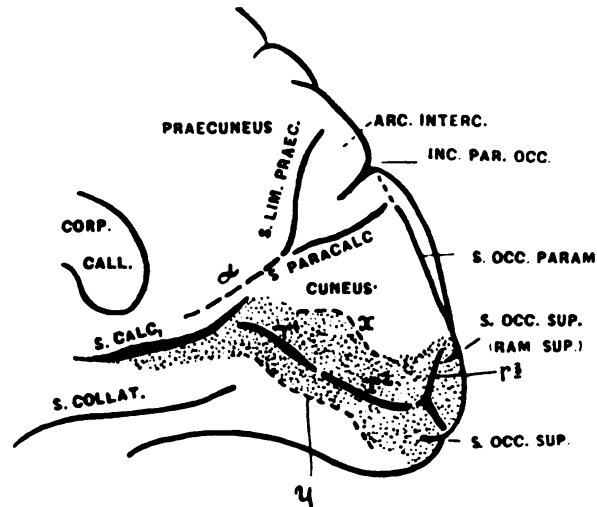


FIG. 5.—Diagram after Elliott-Smith, to show the arcus intercuneatus, the incisura parieto-occipitalis, and the sulci paracalcarinus and limitans praecunei, seen on holding apart the lips of the internal parieto-occipital fossa. The dotted area is the striate area.

The arcus intercuneatus is bounded in front and behind by the sulcus limitans praecunei and the sulcus paracalcarinus, respectively. These sulci may turn over the supero-mesial border, and cut into the arcuate gyrus, and either separately or together and either with or without the incisura parieto-occipitalis, may form the external parieto-occipital fissure.

Dr. Flashman¹ states that in the brains of four Australian aborigines the external parieto-occipital fissure was represented by two fissures continued on to the outer surface of the hemisphere from the internal parieto-occipital fissure, of which these two fissures form the upper bifurcated end, and that in Europeans the external parieto-occipital

¹ Four brains of Australian aborigines. The evolution of the parieto-occipital fissure as illustrated in some aboriginal brains. By J. Froude Flashman, B.A., B.S., M.D. Report from the Pathological Laboratory of the Lunacy Department, New South Wales Government, vol. I., part 1.

fissure is formed by the anterior of these two fissures, the posterior disappearing. The European arrangement is said to be due to an increased development of the parietal lobe in the neighbourhood of the external parieto-occipital fissure, and to a consequent pushing backwards and inwards of the two parts of this fissure, so that only the anterior part remains on the outer surface, whilst the posterior disappears. It would not be expected, however, that an increase of cortex would cause the disappearance of any sulcus, but rather that it would cause a deepening of the sulcus, and this is probably what happens in those cases in which the paracalcarine fissure is found in the internal parieto-occipital fossa and not on the outer surface.

The arrangement of the external parieto-occipital fissure in the brains of the four Australian aborigines is apparently identical with that found in the left hemisphere of brain No. III., described above, the anterior and posterior branches of the internal parieto-occipital fossa undoubtedly being the sulcus limitans præcunei and the sulcus paracalcarinus respectively of Elliott-Smith. The right hemisphere of the Chinese brain No. III. shows a condition half-way between that of the Australian aborigines and that of the European. In this hemisphere both the sulcus limitans præcunei and the sulcus paracalcarinus are present, but the former is the larger and is continued outwards to form the external parieto-occipital fissure, whilst the latter is very small, and ends just external to the supero-mesial border.

A "generalised" external parieto-occipital fissure would be that condition in which all three fissures, the sulcus limitans præcunei, the incisura parieto-occipitalis, and the sulcus paracalcarinus, extend for an equal distance (say one inch) outwards from the supero-mesial border. In these Chinese brains the nearest approach to this condition is in the right hemisphere of the brain from Singapore.

If then there are three fissures which may take part in the formation of the external parieto-occipital fissure, and if any one of these three fissures may be either present or absent, there are, excluding the hypothetical case in which there is no external parieto-occipital fissure, seven

possible arrangements by which the external parieto-occipital fissure may be formed (since the number of combinations of "n" things taken any number at a time is $2^n - 1$, and in this case $n = 3$).

Of these seven combinations which are possible, in twelve hemispheres of the Chinese brains six different combinations were actually found. Specimen A, the left hemisphere of a Chinese brain, was not thoroughly examined.

The most usual arrangement was found to be that in which the external parieto-occipital fissure is formed by the incisura parieto-occipitalis alone. This was found in five hemispheres. The hemispheres are Nos. V. R., II. R., V. L., VI. L., and IV. L.

In one case the external parieto-occipital fissure was found to be the direct continuation of the sulcus limitans præcunei. This hemisphere is No. III. R.

In two cases the sulcus paracalcarinus was found to be continued over the supero-mesial border on to the outer surface to form the external parieto-occipital fissure. These cases are Nos. VI. R. and II. L.

Thus in eight of the twelve hemispheres the external parieto-occipital fissure was found to be the continuation over the supero-mesial border on to the outer surface of one alone of the three fissures.

In one case the external parieto-occipital fissure approaches the "generalised" type, that is to say, all three formative fissures run out on to the outer surface. This was found in the right hemisphere of the brain from Singapore.

In two cases the external parieto-occipital fissure appears to be similar to that just described as prevailing in the brains of the Australian aborigines. That is to say, it is formed by both the sulcus limitans præcunei and sulcus paracalcarinus, which are continued outwards over the supero-mesial border for an equal distance, and appear to be the bifurcated upper end of the internal parieto-occipital fissure.

These two cases are the left hemispheres of No. III. and of the brain from Singapore.

In one case the external parieto-occipital fissure was found to be formed by the continuation outwards over the supero-mesial border of both incisura parieto-occipitalis and of the paracalcarine fissure. This hemisphere is No. IV. R.

The particular combination which was not found in any one of these twelve Chinese hemispheres is a combination in which the sulcus limitans præcunei and the incisura parieto-occipitalis would both be continued over the supero-mesial border on to the outer surface.

SUMMARY VIII.

The sulcus lunatus.—In seven cases, namely, the hemisphere A., VI. L., II. R., II. L., III. R., III. L., IV. R., IV. L., there is a very clear sulcus lunatus. See fig. 1.

In the right hemisphere of the brain from Singapore the sulcus lunatus may perhaps be represented by the transverse sulcus produced by the bifurcation of the pars horizontalis of the intraparietal sulcus.

In V. R. (see fig. 3), V. L., VI. R., and the left hemisphere of the brain from Singapore, the sulcus lunatus is absent. Thus the sulcus lunatus in these cases is not more commonly present on one side of the brain than on the other. In one case only is it certainly, and in one case doubtfully, present on one side and absent on the other in the same brain. Thus it is present on VI. L., and absent on VI. R., and it is perhaps present on the right side of the brain from Singapore and absent on the left side.

In those cases in which the lunate fissure is present, both the retro-calcarine fissure and the line of Gennari extend round the occipital pole on to the outer surface for a greater distance than in the cases in which the lunate fissure is not present.

This is shown by the following tables, which give the distances to which the retro-calcarine fissure and line of Gennari extend forward round the occipital pole on to the outer surface, measured from the occipital pole.

Cases in which the sulcus lunatus is present :—

Brain.	Retro-calcarine fissure.	Line of Gennari.
VI. L.	3.5 cm.	2.5 cm.
II. R.	2 cm.	3.5 cm.
II. L.	Ditto	Ditto.
III. R.	Ends on outer surface of pole	5 mm.
III. L.	2.2 cm.	2.5 cm.
IV. R.	1 cm.	2 cm.
IV. L.	Cut away before examination	3.3 cm.

Cases in which the sulcus lunatus is absent :—

Brain.	Retro-calcarine fissure.	Line of Gennari.
V. R.	Does not reach pole	1 cm.
V. L.	Cut away	1 cm.
VI. R.	Ends on mesial aspect of pole	Ends at pole.
Left hemisphere of brain from Singapore)	Does not reach pole	3 mm.

In the right hemisphere of the brain from Singapore in which there was a doubtful sulcus lunatus, the retro-calcarine fissure extended forward from the pole on the outer surface of the occipital lobe for 4 mm., whilst the striate area extends forward for 5 mm.

Dr. Mott wishes to express his grateful acknowledgements to Dr. H. Fry for the trouble he has taken in obtaining these brains and forwarding them to England.

TWO CASES OF AMAUROTIC DEMENTIA (IDIOCY)
AND A CORRELATION OF THE MICROSCOPIC
CHANGES IN THE CENTRAL NERVOUS SYS-
TEM, WITH THE RESULTS OF A CHEMICAL
ANALYSIS OF THE BRAINS.

BY F. W. MOTT, M.D., F.R.S.

THE reports of these two cases will be found to confirm the clinical observations of previous observers. Moreover, in few essentials do the results of the *post-mortem* observations and the histological investigations differ from those of previous records. Dr. Gordon Holmes has recently published in *Brain* a valuable report on the histological changes in the central nervous system, as the result of the investigation of three cases, with which my observations in the main agree. There are a few points in the histological investigation of the two cases which I am reporting here, which I may mention, however, as being of importance. Not only the posterior spinal ganglion cells, but also *the sympathetic ganglion cells* show the characteristic disappearance of the Nissl substance; it is therefore probable that every nerve cell in the body is thus affected more or less. It may therefore be inferred that the morbid process is a metabolic disturbance affecting the whole of the neural elements, and is not dependent upon inborn morbid anatomical conditions or post-natal changes in the nutrient vascular or interstitial supporting structures of the *central nervous system*.

The fact that it affects the children of Jewish parents, suggests that it owes its origin to some racial inborn tendency to neuronie decay, probably associated with some exciting or predisposing factor connected with an altered condition in the chemical composition of the blood, whereby the normal bio-chemical interaction of the nucleus

on the cytoplasm and the environmental lymph of the neuron is interfered with. "A cell nourishes itself and is not nourished," is as true for the highly complex and specially differentiated nerve cell, with its multiple processes and their arborizations, as for a simple unicellular organism. The nucleus is the trophic centre of the nerve cell, and possesses the specific inherent energy upon which the cell depends for its vital activities and durability. We may therefore suppose that this extraordinary neuronic regressive metamorphosis is brought about by a conspiracy of morbid factors, viz., an inherent racial lack of specific neuronic energy and some general alteration in the chemical composition of the blood, either by the existence in it of a neuro-toxin or the failure of some chemical substance in sufficient quantity for the building up of the nucleo-proteid substance of the nervous system.

Jewish children are usually breast-fed, and the two cases I record, and most of the other cases, have been breast-fed. It would be interesting in any future case to make a careful chemical examination of the milk of the mother. In Case II. the morbid changes found in the liver and pancreas (*vide* photomicrograph), as well as the alimentary canal epithelium, suggest a toxic cause. Syphilis, apparently from the history, could be excluded.

That the very striking inflammatory changes in the pancreas and liver with glandular necrobiosis are not the cause, seems warranted from the statement of Gordon Holmes that in one of his cases none of the viscera showed any macroscopic or *microscopic* signs of disease. Moreover, these morbid changes in Case II. may have been caused by scarlet fever.

This does not, however, preclude the possibility of an absorption of some intestinal-produced poisons.

The following facts appear to show that the essential characteristic of this disease is primarily a failure in the elaboration of the nucleo-proteid of the neurons of the whole body. This substance, which in stained sections appears to lie in the interstices of the fibrils, is, in the living cell, a plasm. It readily stains with basophil dyes

like the nucleolus and nuclear membrane, and it forms the Nissl¹ pattern.

There is a progressive disappearance of the basophil staining interfibrillary substance of the neuron occurring centripetally towards the nucleus, so that as a rule if there is any basophil substance remaining it is in the form of a more or less distinct halo around the nucleus (*vide* figs. 3 and 4, plate II., and photomicro 1). Held was the first to point out that this Nissl substance is a nucleo-proteid. Besides its property of staining with thiazin dyes, Held found that it is soluble in dilute alkalis, leaves a residue on peptic digestion, is not acted on by acids, is insoluble in alcohol ether or chloroform and gives no reaction with Millon's reagent; it gives, however, positive reaction for phosphorus; and Scott found that it contains both phosphorus and iron in organic combination. Repeating Held's tests, Scott comes to the conclusion that there is no doubt about its nucleo-proteid nature. The correlation of the chemical analysis with the histological findings in these two cases supports strongly this view.

Scott in his interesting paper asserts that a transformation of the Nissl substance into the neurosomes of Held has also been established, or, at least an interdependence of the amount of the Nissl substance and the number of neurosomes has been observed. He looks upon the Nissl substance found in the body of the cell and the dendrons as prozymogen and that this is homologous with the prozymogen of secreting gland cells; the substance at the neurosomes or points of contact or synapses of neurons is a substance homologous to the zymogen. This analogy appears somewhat hypothetical, but it is probable that the Nissl substance is the antecedent of another substance which lies at all the points of contact of one neuron with

¹ The differentiation of the cytoplasm which is seen in stained preparations, whether prepared by injection of methylene blue *intra vitam* or by staining sections or films from *post-mortem* material, has not been definitely proved to be the condition which exists in the living neuron as it functions in the body. For if by the *intra vitam* method the Nissl pattern is seen in a film preparation, it may still be argued that this is an indication of a death process.

another, and forms the bio-chemical basis of neuro-potential. All vital processes in cells have a chemical basis, and the process of neural action is chemical, though of its nature we know but little. Either a conductile fibrillary *continuum* exists through systems of neurons from peripheral sense organ to muscle or gland forming simple or complex reflex circles through association systems: or, if we accept, as I do, the neuron doctrine, there are gaps in this fibrillary conductile substance at all the points of contact of one neuron with another in the various systems and communities of neurons which are functionally correlated. These gaps in the fibril structure are filled up by a relatively unstable substance, and each neuron in a system is successively stimulated by chemical changes in this substance at all the infinity of points of contact. There is thus a physiological if not an anatomical *continuum*. Professor Gotch in his interesting and philosophical address to the Physiological Section at the British Association, 1906, says in connection with this subject: "Whether the central termini of neuron processes are in reality joined by extremely fine fibrillar elements, or whether they end blindly in mere juxtaposition, it is undoubted that the functional synapsis presents peculiar features. The chief peculiarities of synaptic activities as distinct from the activities of the nerve fibres are the following: Marked retardation in the maximum rate of propagation, irreciprocity of conduction, which is favoured in the natural or homodromus direction, whilst in the unnatural or heterodromus direction it is obstructed or completely blocked; susceptibility to fatigue, special susceptibility to stimulation and impairment by definite chemical substances, by strychnine, absinthe, anæsthetics, &c., the presence of a resistance which diminishes rapidly when subjected to the assault of a series of entering or centripetal nervous impulses even when each member of the series is quite alone unable to force a passage. All these peculiarities are more or less demonstrable in all nerve endings, peripheral as well as central, and presumably therefore related to the character of the propagation which occurs in the finely divided non-medullated twigs or

"arborizations" into which the nerve fibres break up in such endings and *possibly to some further receptive substance lying beyond the endings*. The Nissl substance may, as Scott suggests, be the antecedent of this substance.

In these two cases it has been shown by chemical analysis that there is a great diminution of nucleo-proteid in the brain and an increase of simple proteid. Until a chemical analysis by the same methods has been made of the normal brains of children of the same ages, the enquiry may be considered incomplete, but this enquiry is now being undertaken. The results of the analysis by Mr. Mann, however, so completely accord with the histological observations, that *two essential points* concerning the chemical changes in the brain may be regarded as proved, viz., the diminution of nucleo-proteid and the increase of simple proteid. For the nucleo-proteids in the brains of children will probably, as in other young and embryonic tissues, be relatively in greater abundance than in the adult tissues. Such a very considerable loss of nucleo-proteid, then, as was found in these cases as compared with adult brain tissue may even represent less than the real loss when the analysis is compared with brain tissue of a similar age.

The older child's brain, Case I., in which the clinical symptoms and the morbid changes were both much more advanced, yielded much less nucleo-proteid and more simple proteid than the brain of the child Case II., in which the clinical symptoms and the morbid changes were less advanced.

The loss of nucleo-proteid may be correlated with the loss of the basophil chromatic Nissl substance, a nucleo-proteid derivative of the nucleus. The increase of simple proteid with the increase of neuroglia, particularly the neuroglial fibrils which were found in great abundance in the superficial areas of the cortex gives it the tough, leather-like consistence. The more obvious the Weigert-stained fibrils and the fewer the nuclei relative to the amount of fibrils the older is the process of neuroglial proliferation; consequently, the less the nucleo-proteid the more the simple proteid.

The complex convolutional pattern met with in these cases is not in accordance with the term idiocy. I have therefore termed the disease amaurotic dementia.

The large size of the convolutions of Case I., the narrow sulci and the very heavy weight of the brain, 1,400 grams, show that in this case (of longer duration than Case II.), there was something more than replacement of the neural elements by neuroglia tissue; there was, indeed, a hypertrophic gliosis more than necessary for mere substitution of space occupied by the neural elements. In fact, it seems to indicate a formative proliferation of a denser tissue which would partly account for the heavy weight of the brain.

The hemispheres in Case I. relatively to the total weight of the brain were 70 grams in excess, indicating that the hemispheres were more affected in this respect than the pons and cerebellum. In Case II., comparatively speaking, none of these changes were so apparent, and the brain weight was about normal for a child of that age.

The macroscopical and microscopical changes of the brains correlated with the two essential results of the chemical analysis may be summarised thus:—

CASE I.

<i>Histological.</i>	<i>Naked Eye.</i>	<i>Chemical.</i>
Abundance of Weigert fibres; abundance of branching neuroglia cells; complete absence of Nissl granules and destruction of nuclei of ganglion cells.	Substance very dense and firm; brain very heavy, cortex greyer than natural. Convolutions broad, flattened, and sulci narrow.	Nucleo-proteids largely diminished. Simple proteids largely increased.

CASE II.

<i>Histological.</i>	<i>Naked Eye.</i>	<i>Chemical.</i>
Abundance of neuroglia cells; Weigert fibres not marked. Absence of Nissl granules, but nuclear and cell destruction not so advanced as Case I.	Brain weight about normal; substance of cortex denser than natural; convolutions not flattened or broader than natural; sulci not especially narrow.	Nucleo-proteids diminished. Simple proteids increased.

Case I.—Female child of Russian Jews, was found to be blind at 12 months, and suffering with a progressive weakness of the limbs with rigidity, followed by complete paralysis, except of the automatic functions of sucking, swallowing and breathing: and hardly any sensory response to surroundings. Death, aged 1 year 10 months. Brain only examined. Weight 1,403

grammes. Convolutional pattern good, cortex extremely firm and leather-like in consistence, central white matter semi-fluid, like cream in places. Microscopic examination:— Similar changes to those previously described. Chemical examination:— Simple proteids increased; nucleo-proteids greatly diminished.

Case notes.—R. T., female child aged 1 year 6 months, admitted to Charing Cross Hospital under my care, June 18, 1905. Parents Russian Jews, not related, married ten years, three children, aged 7, 4, and 18 months respectively. Two elder children are quite normal. No miscarriages. Instruments with first child. Illness began twelve months ago—apparently general weakness came on insidiously—later, patient had frequent convulsions, in which the legs and arms were quite rigid. There is some doubt if patient was not blind at birth, it certainly was when it came under the care of a medical man about 6 months ago.

Condition on admission.—Weight, 1 stone, 4 lbs. Well nourished, well developed.

Bones.—Anterior fontanelle not closed. Upper and lower central incisors present. Thorax and spine seem normal, no evidence of rickets. Long bones seem normal, no evidence of rickets or syphilis. Child lies supine on her back, and never moves voluntarily. She rarely cries.

Chest.—Resonant on percussion. On auscultation numerous râles can be heard over both sides, anteriorly and posteriorly. Heart sounds normal.

Abdomen.—Resonant on percussion—no free fluid. Liver not enlarged, spleen not palpable.

Muscles and movements.—Muscles of legs and arms are quite flaccid. They seem incapable of being moved voluntarily. There is not much apparent wasting, the limbs being well covered with fat. Feet are in a position of talipes equinus. Knee-jerks present. Plantar stimulus gives *extensor response*.

Mouth.—Tongue normal, no rhagades at corners of mouth.

Skin.—No eruptions.

Eyes.—Marked atrophy of outer half of each disc, and at each macula a dark brownish red spot, surrounded by a white zone. Typical appearance of amaurotic idiocy. Pupils are equal and regular, both react to light (E. T. Collins).

June 19, 1905.—Patient has a yellowish discharge from the eyes. Patient starts if a noise is made close by. She grinds her teeth for a few minutes at a time. Moved arm above head.

June 20, 1905.—Weight, 1 st. 4 lbs. Discharge from eye continues. Cried a good deal last night. Patient has started on two occasions when some article has fallen in the ward, and on

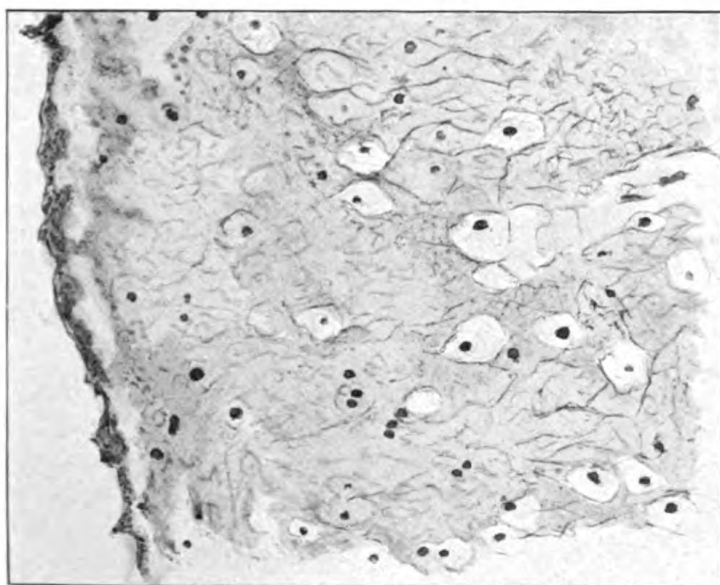


FIG. 1.

Section of the cerebral cortex from the ascending frontal convolution. Case I. stained by Belchowsky method.

FIG. 1. Shows the superficial layers of the cortex with the pale unstained pyramidal cells; the nucleus alone is stained. The cells are oval, pyriform, closely connected and sometimes fused together; the only fibrillary structure is the intercellular substance which mainly consists of neuroglia fibrils. Magnified 300×1 .

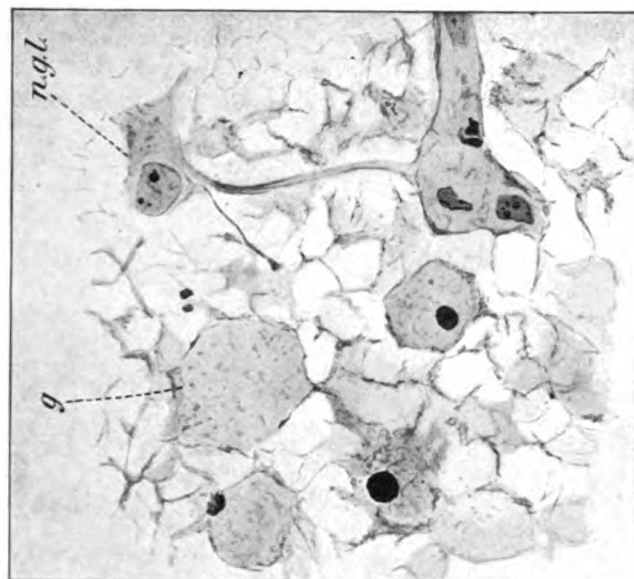


FIG. 2.

The section in the deeper part examined with oil immersion Apochrom. Zeiss 1.40 mm., ocular 4. Two globose ganglion cells (*g*) are seen fused together by a narrow isthmus. Many neuroglia cells with branching processes forming a reticulum are seen, and one sends a process on to a small blood vessel. Magnified 700×1 .

1000

one occasion screwed up her face as if she was going to cry, and made a very feeble whimpering sound. Grinds teeth occasionally. Eyeballs move continually, frequently upwards, so that only the sclerotics are visible. Right eye closes more perfectly than left. Right hand is usually closed, index finger less flexed than the others. Patient does not notice a lighted match. Pupils react to light. Arms occasionally become somewhat rigid for a few minutes.

June 22, 1905.—Patient continues to lie in same position. No voluntary movement of limbs, but if a leg is abducted, clonic movements occur. Knee jerks present. Well marked extensor response, followed by movements of the legs. Right hand maintained in same position as in last note. Left hand, fingers semi-flexed, thumb in palm of hand. Movement of eyeballs as before.

June 29, 1905.—Patient has looked somewhat pale during the last two days. The rolling movements of eyeballs, blinking movements of eyelids, and grinding of teeth still continue. The eyelid movements sometimes continue for three or four minutes, at the rate of about 100 per minute, with slight pauses for a few seconds, during which no movements occur. The right hand is maintained in the position mentioned before, and left thumb is now definitely flexed in palm. Patient yawned to-day three times. There has been no loss of weight during the past week.

July 3, 1905.—Patient does not look so pale—otherwise there is no change.

July 12, 1905.—Left lateral nystagmus this morning—no other changes.

August 11, 1905.—Patient remains with practically no change in her condition, but she is paler, and seems to be getting gradually weaker. Still slight discharge from her eyes. Her apathetic attitude still continues, but occasionally she utters a short whimpering cry, more frequently of late than formerly. There are slight convulsive twitchings of the mouth and lips. Pupils remain widely dilated, and react sluggishly to light.

August 18, 1905.—Much wasting of all the muscles. Patient remains lying in the position in which she is placed, and never moves voluntarily. There is no longer rigidity of the limbs. She lies generally on her back, with her legs closely approximated and parallel to each other. There is marked talipes equinus, her feet are blue and cold.

August 25, 1905.—There is still some discharge from her eyes, which appear deeply sunken. There is considerable wasting of the muscles of the face, which is thin and pale.

Nystagmus of the eye continues—sometimes laterally, sometimes vertically. Sometimes patient rolls her eyes upwards so

that only the sclerotics are visible. There is more or less constant champing of the lips and grinding of the teeth. Patient has cut the upper and lower lateral incisors. She takes no solid food, but will drink milk readily, only from the feeding bottle, however.

September 2, 1905. Patient is constipated and requires regular doses of pulv. glycyrrh. co. to keep the bowels open. She passes urine involuntarily under her. This condition has existed ever since admission. Her head gives one the impression of being too large for her body. The anterior fontanelle is still open, there is no bulging, and it seems situated rather far back, as though the frontal bone was unusually large.

September 9, 1905.—There is no obvious strabismus. The pupils are equal, widely dilated and *unresponsive to light*.

The sensitiveness to sound observed on admission still continues. Patient starts when anything is dropped in the ward. Respirations average about 32 to the minute, highest 44 (except on one occasion when rate was 60) lowest 24. This rate has been maintained ever since admission. Pulse average 104, highest rate recorded 140. Patient breathes quite easily, there is no dyspnoea. Temperature during last week rose on one occasion to 100° F., it has risen to this height only on four other occasions since admission. On every other occasion in which it was taken it has been subnormal.

September 16, 1905.—Condition of patient much the same, except that she is obviously getting weaker and more emaciated. Her appetite—for fluids only—remains good; she drinks about 3½ pints of milk daily. She cries only on being moved. Blinking movements of the eyelids continue, not constantly, but paroxysmally, numbering about 80 to the minute. Occasionally she has tonic spasms of the muscles of the arms and legs, each spasm lasting fifteen or twenty seconds, but generally the limbs are quite flaccid. There is no retraction of the head.

September 23, 1905.—Patient lies to-day supine on her back, with legs fully extended, and feet in position of talipes equinus. The arms are extended by her side and the fingers firmly flexed into the palms. This position of the hand has obtained for some days past, so much so, that pads of cotton wool have been placed in the hollow of the palm to prevent the nails injuring the flesh. There is a tendency to the formation of bed sores over the lower part of the sacrum and the great trochanters of the femora.

September 29, 1905.—During the past week some difficulty in swallowing has been noticed. This is not constant, only occasional. Patient will keep milk unswallowed in her mouth for quite a long time—especially at night. There has been no sickness. To-day she is lying on her right side. The left lower limb is adducted and overlaps the other. It is flexed at the knee; the

right lower limb is perfectly straight in the bed. There is slight spasticity in both legs. Knee jerks are present. No ankle clonus. The pupils are widely dilated, equal and regular, and do not react to light. The contracture of the hand noticed above still continues. Anterior fontanelle still open—no bulging palpable. The skin is broken over the lower part of the sacrum and over the right great trochanter.

October 30, 1905.—Death.

Post-mortem notes.—Partial examination only. Permission of the parents was obtained by the Rev. Mr. Singer to examine the brain. Female child, emaciated. Well-marked contracture of all four limbs. The upper limbs are extended and partly everted. Fingers strongly flexed, also thumbs in palms of hands. Legs extended and adducted. Feet *dropped*. Toes adducted and strongly flexed. There is a slight sacral eschar, no bed sore. P. M. rigidity has passed off, no p.m. staining of dependent parts. Muscles are of good colour. The skull is thinner than normal, there is wide inter-parietal development, but the inter-parietal suture is closed, no bosses. Anterior fontanelle is still open for about 1 inch. The dura mater is normal, no excess of subdural or subarachnoid fluid. Membranes normal. The convolutional pattern is complex; the convolutions are broad and flattened, and the sulci are correspondingly narrow and filled up. The substance of the brain in the frontal, central, and temporal regions is much firmer in consistence than natural. The cortex feels like leather or india rubber, covering a softer substance within. Weight of total brain = 1,403 grammes; weight of two hemispheres = 1,276 grammes; weight of pons and cerebellum = 166 grammes $\times 8 = 1,328$ grammes. The optic nerves and optic tract are atrophied. The ependyma of the fourth ventricle is smooth.

Histological changes.—Sections of the following tissues were made by the usual methods for displaying cell and fibre structure, both neural and neuroglial:—

- (1) Various regions of the cortex cerebri with subjacent white matter. Optic thalamus and corpus striatum.
- (2) The spinal cord and spinal ganglia.
- (3) The optic nerve and retina.

The following stains were used: Nissl, polychrome and eosin. Weigert for fibres, Weigert for glia tissue, Heidenhain and eosin. Eisath and Mallory stains for glia cells and fibres. Bielchowsky for neurofibrils. The naked eye appearance of the sections showed a profound atrophy of the subcortical white matter, the cortical grey matter was thicker than natural. Microscopical examination of the orbital, first frontal and central convolutions shows profound changes by all the methods mentioned. Not a healthy cell can be seen; in places it is very difficult to determine which cells are

PLATE II.

Fig. 1.—Transection of a small vessel of the cortex with surrounding lymphatic showing leucocytic infiltration of the adenoid reticulum, and especially proliferation of the nuclei of the endothelial cells. Specimen stained with polychrome and eosin. Magnification 500.

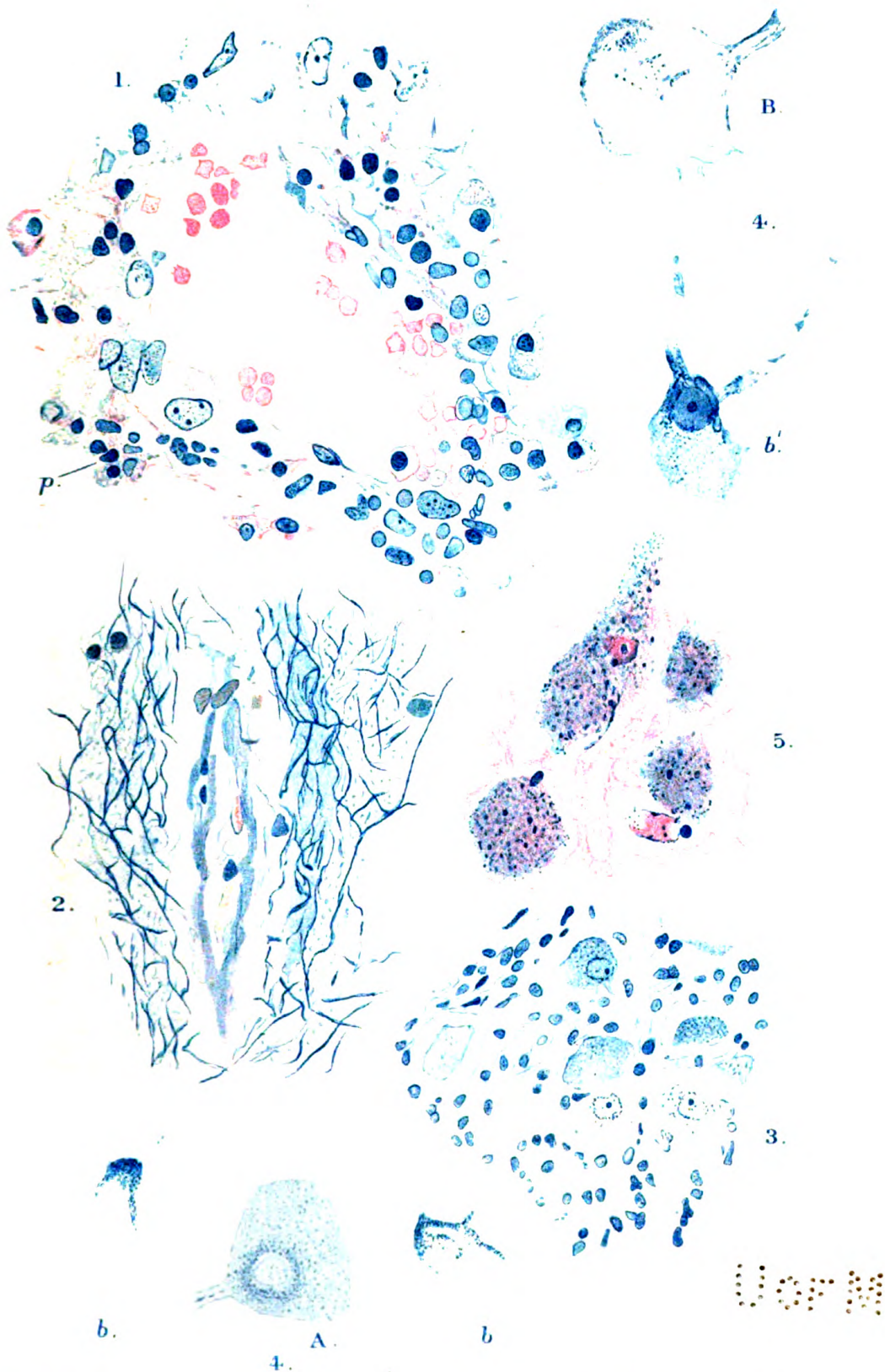
Fig. 2.—Section of superficial region of cortex, Case I., stained by Weigert's neuroglia fibril method. The dense plexus of fibrils seen around a small vessel. Magnification 500.

Fig. 3.—Section of sympathetic (cervical inferior) ganglion, showing the partial disappearance of the Nissl granules. Magnification 200.

Fig. 4.—Various cells. Magnification 500. (A) Anterior horn cell of the spinal cord showing a halo of fine nucleo-proteid granules around the nucleus. All the processes have apparently disappeared; possibly owing to swelling of the cell they are not in the same plane of the section and therefore do not appear.

(B) A giant Betz cell showing disappearance of chromophilous substance; (b) two cells showing curious distribution of chromophilous substance at one end of the cell apparently in *b'*, this is related to the disturbance of the nucleus from its normal position in the cell, and as the nucleus is not seen in the other two cells the same reason may have led to the disposition of the Nissl substance in them.

Fig. 5.—A group of pyramidal cells of the cortex distorted in shape, and two of them are fused together so that the two nuclei are touching. These cells are apparently in a state of coagulation necrosis, the protoplasm is stained a diffuse, dirty, pinkish purple, owing to small particles of varying size taking the two stains. Magnification 500.



ganglion cells and which neuroglia. As a rule the pyramidal cells are seen packed close together and sometimes appearing, as it were, fused into one another. Their shape is altered, they are no longer pyramids, but globular ovoid with pointed ends, *vide* fig. 4, plate ii., oval, or irregularly quadrate. The body of the cell is stained a faint pink by polychrome and eosin; by the methylene blue it is generally unstained. In some cells the nucleus is present only faintly stained, the nucleolus alone in some cases taking the blue stain. In many of the cells the cytoplasm is filled with a dust of fine particles, stained pink or a purplish pink. Numbers of uniformly purple-stained nuclei are seen lying in the shadow-like forms of the ganglion cells. Many nuclei and neuroglia cells are seen. The giant Betz cells at the top of the ascending frontal may in a few instances show a little chromatic substance, *vide* fig. 4, plate ii.; but in no instance was there any evidence of a Nissl pattern. The remaining Betz cells were only visible by their outline, and they exhibited just a little chromophilous substance at the apical end. Owing to the distorted shape of the ganglion cells and the readiness with which their cytoplasm takes the eosin stain, it is very difficult to differentiate them from neuroglia cells. In the molecular layer of the ascending frontal and parietal cortex, numbers of branching glia cells can be made out quite distinctly, and these in no way differ in appearance from those seen in the deeper layers among the cells. The nucleus alone, however, of these glia cells stains with blue, the cytoplasm and its branching processes continuous with a reticulum are stained a faint pink. There are a large number of glia nuclei at all levels. Stained by Weigert's method the dense leather-like conditions of the superficial cortex is explained, for it consists almost entirely of a dense network of neuroglia fibrils, *vide* fig. 2, plate ii. and photomicro. ii. This is especially evident in the more superficial layers. There was no apparent diminution in the number of the cells; they seemed, indeed, to be more closely packed together than normal.

The Spinal Cord.—There is throughout the grey and white matter nuclear proliferation, partly derived from proliferated glia cells, partly leucocytes; the anterior horn cells show the characteristic chromolytic change in a less marked form, so also the spinal ganglia. The chromophilic substance is not seen on the dendrons or at the periphery of the cytoplasm, but a zone of basophil substance of varying extent is discernible around the nucleus, *vide* photomicro. i. In many the nuclear membrane and nucleolus has disappeared and only a patch of basophil substance marks the former position of the nucleus; in others the nucleolus and nuclear membrane is stained deeper than the rest of the cells, rendering the nucleus visible with a halo of fine basophil-stained particles around. In some cells the nucleus is stained purple

throughout, the nucleolus and nuclear membrane being visible by deeper staining. There is a marked subpial and septal proliferation of glia tissue throughout the spinal cord, especially marked in the long cerebral and cerebellar tracts.

The retina.—On removing the retina from the back of the eyes, probably owing to the thinning of the layers caused by atrophy of structure, a small hole, the size of a pin's head, was found at the macula. There was no choroid attached, yet there appeared a brown spot? This brown colour disappeared very soon after the retina was mounted in Farrant's solution. I used one retina for mounting thus, the other I hardened in 5 per cent. formol and cut sections through the macula after embedding in paraffin. The sections were cut of 5 μ and 10 μ thickness and stained with Nissl polychrome and eosin. The small hole was found. The only structures visible throughout the sections were, portions of retinal vessels, the hyalin membrane, the fibres of Müller, the plexus of fibrils which support the essential structures of the retina and the outer and inner layer of granules. Here and there rods and cones are seen on the surface, and occasionally altered ganglion cells—or rather the remains of them, for nowhere could I find anything more than an occasional mass of diffusely stained protoplasm, unrecognisable as a ganglion cell if it were not for the fact that they were, when seen, located in the proper situation, and resembling in appearance the altered ganglion cells seen in the cortex. Frequently aggregations of these cells were seen as if fused and blended with one another. Practically all the visual protoneurons have in this case disappeared or have been destroyed. Transections of the optic nerves stained by various methods, including Weigert's, showed only a few fibres left, and these were mostly fine fibres and irregular with varicosities.

In the cortex cerebri many of the vessels were surrounded by proliferated nuclei; examined with an oil immersion these were seen to be endothelial cells undergoing active proliferation (*vide* fig. 1, plate ii.). The same cells can be observed around the smallest vessels, apparently lying out in the tissues, and it was thought some were engaged in active phagocytosis.

The cortex stained by Bielchowsky's method showed aggregations of oval, ovoid, and round phantom cells, in which often no nucleus was visible, and if any structure in the cytoplasm were visible at all, it was only a very faint network which appeared to be continuous with a coarser and more obvious extra cellular network (*vide* fig. 1, plate i.). Nothing of the nature of definite fibrils coursing through the cells as described by Gordon Holmes in his cases could be observed. This was no doubt accounted for by the much more advanced stage of the disease that this case attained to.

Neuroglia cells and their nuclei can be seen, and their branching processes enter into the formation of the better stained network of fibrils lying between the phantom ganglion cells. The nuclei of the neuroglia cells are stained black, and seem to lie upon, or occasionally even outside the cytoplasm which stains deep grey, and assumes a characteristic asteroid shape; some of the large mesoglia cells send long processes on to the walls of the vessels (*vide* fig. 2, plate i.). In a few instances the protoplasm of the ganglion cells has entirely disappeared and a hollow space apparently bounded by the neuroglia network alone marks its previous site.

Cortex stained by Weigert method.—So advanced is the destruction of the ganglionic elements of the cortex, and so marked is the glia proliferation that the sections were most unsatisfactory. Moreover, the white matter, when the brain was removed, was quite different to normal, being like thick cream. Specimens were, however, prepared. The ganglion cells are darkly stained, and under a high power it is seen that the whole body of the cell, except the nucleus is crowded with purple granules. No super-radial or tangential fibres are seen, but bundles of radial fibres, nearly all of which are varicose and degenerated can be observed.

Spinal cord, stained by Nissl method. The anterior horn cells show the following appearances:—The cells are swollen; their borders are convex rather than concave. The processes are indistinctly seen, and the cells are more closely aggregated together than normal. The cells are faintly stained, or almost unstained. When stained there is no evidence of the characteristic Nissl granules, but only a fine dust-like powder of stained granules, which in the majority of instances are most abundant around the nucleus forming a perinuclear basophil halo of blue particles. The nucleolus and the nuclear membrane are usually deeply stained blue. Every cell of the spinal cord, whether of Clarke's column or the intermedio-lateral tract show this change, but in a less degree than the anterior horn cells (*vide* photo-micro. i.). Throughout the white and grey matter are numbers of nuclei which indicate proliferating young glia tissue. In the regions of the long descending tracts of the spinal cord are abundance of large branching glia cells.

Spinal cord stained by Weigert method. Cervical Enlargement.—There is almost a complete disappearance of fibres with secondary sclerosis in the direct and crossed pyramidal tracts. There is a partial disappearance of the fibres in the antero-lateral and direct cerebellar tracts. With regard to the latter tract their degenerative atrophy is more marked on one side than the other.

There is some sclerosis in the posterior median column. The anterior and posterior roots show comparatively little alteration

although the myelin sheaths seem to be thinner than normal, and do not stain so well. There is also comparatively little degenerative atrophy of the ground bundle fibres surrounding the grey matter.

Mid-dorsal region.—The sclerosis and outfall of fibres is almost limited to the descending pyramidal tracts, but there is some sclerosis of the direct cerebellar tracts.

Lumbo-sacral region.—There is sclerosis and outfall of fibres in the crossed pyramidal tracts, and there is some sclerosis and outfall of fibres in the posterior roots and root zone.

By Marchi method.—There is recent Marchi degeneration in all regions of the cord, but most evident in the posterior roots and their projections into the posterior horn and posterior column.

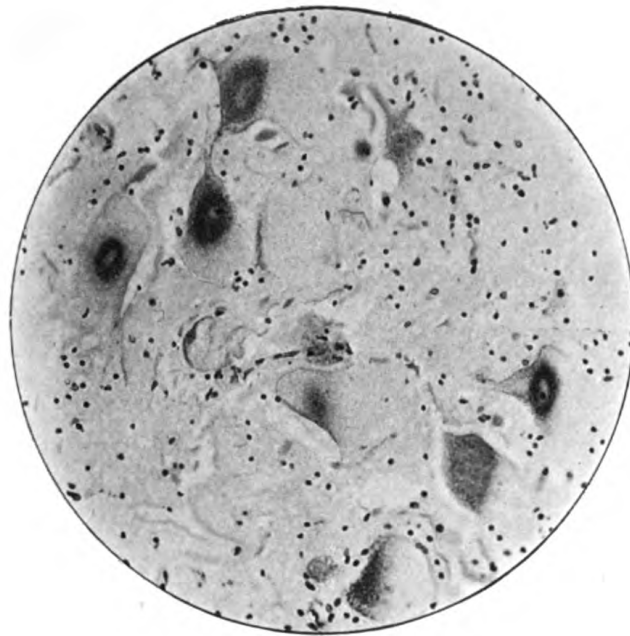
Case II.—Amaurotic family idiocy, under the care of Dr. Coutts and Dr. Eustace Smith, and Mr. Hancock, of the East London Hospital, Shadwell.—Clinical Notes by Dr. S. A. Owen.¹

Summary.—Child of Jewish parents, no consanguinity or hereditary neuropathy ascertained. Characteristic clinical symptoms and histological changes of the central nervous system. Sympathetic ganglia examined, the same change in the Nissl substance discovered. Marked chronic inflammatory changes in pancreas and liver. Convolutional pattern of brain complex. Chemical analysis exhibited a diminution of nucleo-proteid, and an increase of simple proteid, but not so marked as in Case I.

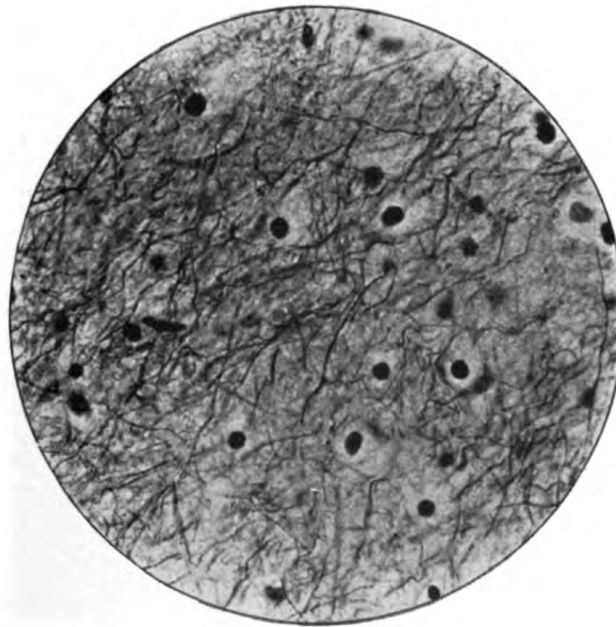
Jack M—s, admitted East London Hospital, January 13, 1906; discharged January 25, 1906; readmitted February 7, 1906; died April 12, 1906. Age on first admission said to be 8 months.

History (given by parent).—Quite healthy at birth, could not pass his water during first twenty-four hours. Doctor had to pass an instrument. Nil drawn off. Passed water normally next day. When 6 months old child developed a rash all over, rash lasted four or five days. Soon after developed pneumonia, being dangerously ill for one week. Had a convulsion during this illness—up to present no other illness. Ever since pneumonia, mother asserts child has not taken notice of things. His attention cannot be attracted. The eyes wander aimlessly. This condition of things was not noted prior to the pneumonia. Mother thinks he cannot hold his head up as well as he should for his age. He

¹ I am greatly indebted to the above gentlemen for allowing me to make the *post-mortem* examination on this case, and to Dr. Owen, the resident medical officer, for the excellent notes he has sent.



PHOTOMICROGRAPH I.

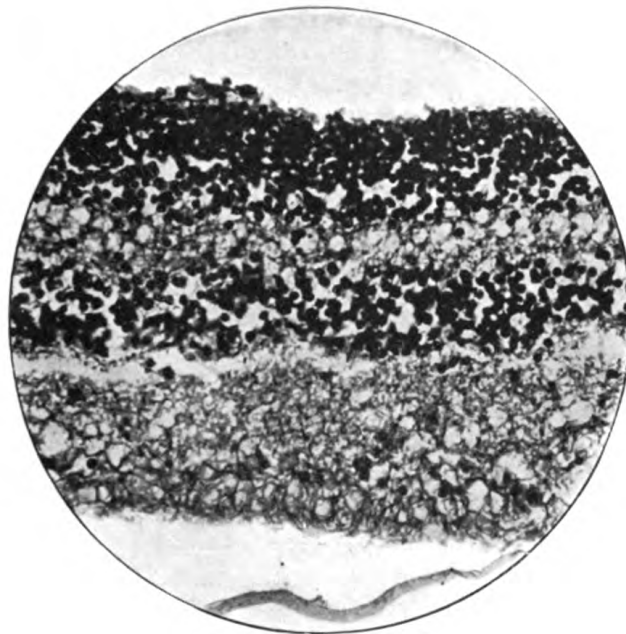


PHOTOMICROGRAPH II.

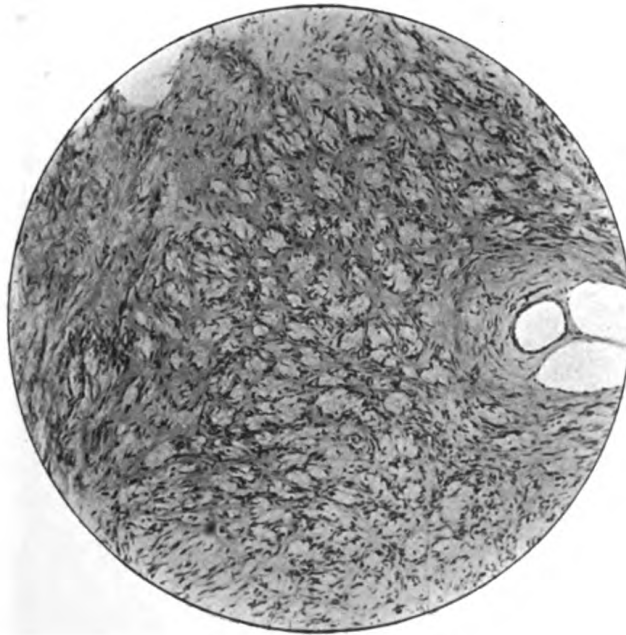
Fig. 1.—Photomicrograph of the anterior horn lumbar region of spinal cord, showing the motor neurons in varying stages of chromophilous retrogressive metamorphosis. Cells in all stages of this retrogressive change can be seen. The neuroglial nuclei are increased. Magnification 200.

Fig. 2.—Photomicrograph of the cortex cerebri, Case I., stained by Weigert neuroglia method, shows dense network of fibrils with neuroglia cells. The nuclei are deeply stained. Magnification 590.

1



PHOTOMICROGRAPH III.

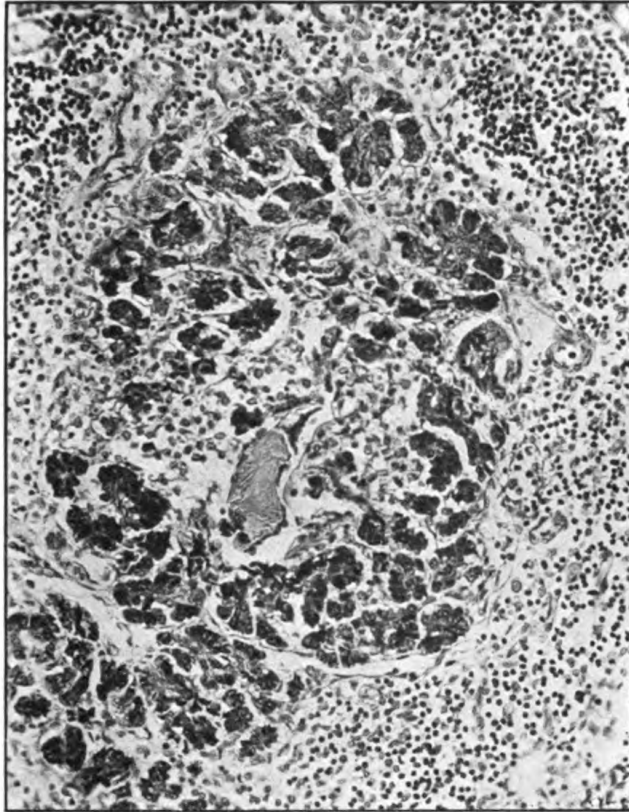


PHOTOMICROGRAPH IV.

Fig. 3.—Photomicrograph of section of retina stained by polychrome eosin method; the hyaline membrane is detached. There is no evidence of ganglion cells and their processes seen. Magnification 330.

Fig. 4.—Photomicrograph of optic nerve at entrance to the eyeball. The nerve fibres have almost entirely disappeared. Magnification 80.

100



PHOTOMICROGRAPH V.

Fig. 5.—Photomicrograph of section of pancreas, Case II., stained polychrome and eosin. An intense interstitial inflammatory change is observed, and this has in one place extended into the inter-acinal structures of the lobule. Under this comparatively low magnification the cells of the acini can be seen to be unequally stained owing to necro-biotic changes. Glycosuria was not observed during life. Magnification 220.

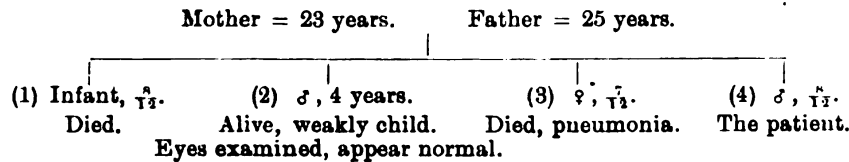
1100

could do this, she asserts, before his illness. Has had an ear discharge since 3 months old, no pain, no blood from ear. Mother thinks lack of hearing power may be responsible for his not taking notice of things. No squint, no white reflex. Has been breast-fed up to the present, no other food; mother whilst suckling has not taken any peculiar diet. Bowels regular. Has never walked or crawled, but could, when 6 months old, stand firmly on his legs when allowed to do so. No convulsions other than that noted above. No definite paralysis. The back muscles appear to be quite strong.

Past history.—Nothing of importance other than that noted above. The confinement was a normal one, and lasted only one hour and a quarter.

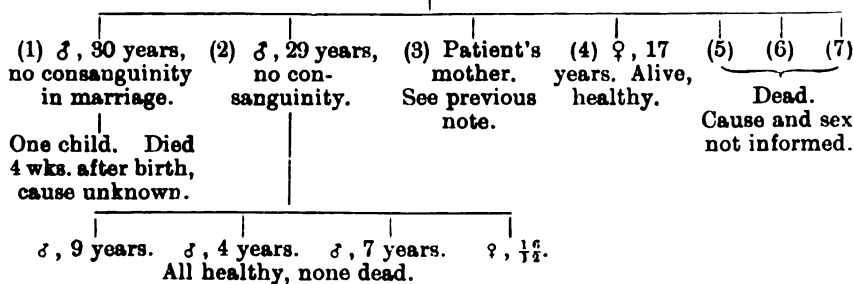
Note.—I am told by Mr. Parsons that this child was brought to Moorfields, City Road, when 6 months old. He was immediately admitted, but developed measles, and was discharged. On enquiry no information was given to him concerning the child's subsequent movements. The parents did not acquaint me with this fact.

Family history.—Parents Jewish. Look healthy. Mother and father no blood relation.



There is nothing to suggest syphilis in parents.

Mother's family.—Patient's great grandparents not known. Patient's grandparents.—Alive, well, no consanguinity.



It is possible that 5, 6, and 7 may have suffered from the disease, otherwise there is no evidence of its being in the family.

Father's family.—Patient's great-grandparents.—No information. Patient's grandfather = 45; grandmother = 45. No blood relation. Alive, healthy.

MALES.

- | | | |
|---|--|---|
| (1) Patient's father, 25 years.
Healthy. | (2) 18 years.
Married; no blood
relation. No family. | (3) 1½.
Healthy as far as
is known. |
|---|--|---|

FEMALES.

- | | | | | |
|------------------------------|--------------------------------------|--------------|--------------|--------------|
| (4) 13 years. | (5) 12 years. | (6) 9 years. | (7) 6 years. | (8) 4 years. |
| Alive, healthy. | | | | |
| (9) 3 years.
Died, croup. | (10) Few weeks.
? cause of death. | | | |

There is absolutely no history of any eye disease, syphilis, or neurosis as far as can be ascertained.

Present state of patient. (Taken soon after admission, in January, 1906.)

General.—Is extremely well nourished, rather pale. Mucous membranes good colour, however. Head good shape (= $17\frac{3}{4}$ inches circumference). Anterior fontanelle widely open. Hair normal. No cranio tabes. The eyes wander aimlessly. His attention, however, appears to be attracted by the ticking of a watch, and he looks in the right direction. The ward sister thinks he follows the light of a lamp if bright enough. When placed in a sitting position his head does not fall about, as if his head muscles were weak. Muscular development appears to be very good. No muscular wasting. Skin normal. Sleeps well. Takes food well. Mother is weaning the child in accordance with our advice. Is an amiable child.

Gastro-intestinal.—Two lower incisors only. Tends to protrude his tongue like a Mongolian. Abdomen is large, but normal in other respects. Spleen not felt, liver not felt. Bowels regular for most part, motions normal.

Thorax.—(Circumference through nipple = $18\frac{3}{4}$ inches) well covered, good shape. Heart negative, lungs negative.

Genito-urinary.—Urine negative to ordinary tests. Uric acid, urea (unusual abnormal products not tested for). Testicles normal.

The central nervous system.—Cranial nerves intact. Pupils, equal in diameter, normal reactions direct and consensual. Eye-movements, good in all directions. No nystagmus or strabismus. Motor, no paralysis or muscular wasting. Sensory, no obvious abnormality, two tests necessarily imperfect. Electrical reactions, not tested. Reflexes, normal for the child's age. Sphincters, normal for the child's age. For ophthalmoscopic examination see report by Mr. Hancock.

Further Progress of the Case up to January 25, 1906.

No appreciable change was noted in the child's condition between his admission and his discharge on January 25. During

this time the eyes were carefully examined by Mr. Hancock, under CHCl_3 .

On January 15, weight was 1 st. 6 lb. 10 oz. On January 21, weight was 1 st. 6 lb.

Temperature.—This once only reached 99° , otherwise was between 98° and N.

Pulse.—Varied between 128-100.

Respiration.—Varied between 44-20.

Bowels.—Regular for most part.

Clinical notes from February 7, when child was readmitted, to the time of his death, April 12, 1906.

After discharge nothing was heard of the child until February 7, when, on enquiry, it was heard the child was very ill. The mother was advised to bring up the child as soon as possible. This she did on February 7. The mother says the child had been well until the first week in February. On February 2, she developed a rash which was said to be "measles." Pneumonia again set in almost immediately.

Present state on admission.—February 7. Child very weak. Still well nourished. Head muscles now obviously weak and head falls back, simulating head retraction. There is no rigidity, however, associated with retraction. There is no obvious muscular wasting. Reflexes are still brisk. Plantar reflex gives extension. The child is too ill to warrant detailed examination of the eyes, but the picture appears to be unchanged. (Mr. Hancock reported soon after admission, February 9, that there was no change in the optic nerve itself.) The child has well marked signs of broncho-pneumonia. The pupils large, but equal. Has cut one more tooth (upper incisor).

February 18.—Since admission has been in a critical condition. Broncho pneumonic signs now clearing up. Stimulants reduced. At times colour gets very bad, and breathing very difficult, lies on back, hardly ever moves. Head muscles weaker than before. Reflexes brisk. Can move head a little from side to side.

February 24.—Still has some bronchitis. Temperature again been irregular. Right arm now appears to be rigid. Is now desquamating profusely. The rash called measles, appears to have been scarlet fever.

February 26 to March 10.—Temperature again very irregular, reaching 103° at times; has been losing weight, viz., February 20, = 1 stone, 4 lbs., 2 ozs.; March 2, = 1 stone, 2 lbs., 8oz.; March 8, = 1 stone, 14 ozs. There is now well marked œdema of the hands and feet. He lies in a drowsy, semi-conscious condition, appears to recognise his mother's voice at times; at others is quite oblivious of his surroundings. Rigidity of the limbs is sometimes marked; at others it is much less evident. Eye examined at inter-

vals; appears to be little or no change. The macular white spot possibly larger. He resents ophthalmoscopic examination and moves his head from side to side on the pillow.

March 10 to 26.—Losing weight, viz., March 15, = 14 lbs., 10 ozs.; March 25, = 14 lbs., 8 ozs. Very bad now, œdema still present, weaker certainly. Temperature much lower level.

March 31.—Passed almost pure blood in urine to-day. Examination shows no casts or crystals. Temperature subnormal last few days.

April 3.—Still blood in urine.

April 10.—Though examined from time to time there is little of importance to relate. Gradually wasting. Still lies in semi-comatose condition. Skin during last few days has been extremely dry. Child now very anæmic. The ears have an alabaster appearance. Still œdema of legs to the knees, with considerable pitting on pressure. Dorsum of hands very œdematous. Face only a little puffy. Skin of face much excoriated and bleeds very readily. Abdomen much sunken. Skin very loose and inelastic. Has fits of crying or whining. Does not know anyone now. Bowels opened two or three times daily. Blood has now disappeared from urine. No vomiting. Rarely moves its limbs, and then only the upper. For temperature, pulse and respiration, see chart.

C. N. S.—Eyes nearly always open. Two nurses say he sleeps well. Eyes wander aimlessly. Does not follow a light. Moans when eyes are examined. Makes no attempt to resist the eyelids being opened. Cornea and conjunctiva covered with mucous at times, but media appear to remain clear. Limbs alternately rigid and flaccid. Lower certainly quite powerless. The muscular wasting is in harmony with the general wasting.

Reflexes.—Knee jerks brisk; never absent at any time Babinski's sign variable.

April 12.—Child died suddenly to-day. The intense anæmia suggests an internal hæmorrhage, ? where.

The eyes were excised immediately after death. One was placed in formalin (weak), the other in absolute alcohol for some hours.

A very thorough *post-mortem* examination was made the same evening, 9 p.m., by Dr. Mott, and specimens removed by him for microscopic and chemical examination.

The pathological report upon the eyes will be given by Mr. Hancock.

AUTOPSY BY DR. MOTT, APRIL 12, 1906, SIX HOURS AFTER DEATH.

The body is emaciated and the legs and feet œdematous. No *post-mortem* staining. The eyes had been removed for examination by Mr. Hancock.

Head.—The anterior fontanelle is closed. The cranium is of normal size and shape, and of average thickness. The dura mater is very adherent to the cranium and separates with difficulty.

Subdural space.—Over the whole of the right hemisphere is a thin film of dark clotted blood, thicker, however, over the orbital and temporal lobes; and after removal of the brain from the skull a layer of blood clot is left in the temporal fossa and over the orbital plate; it has no doubt gravitated there. This hæmorrhage is of quite recent origin, but has flattened considerably the convolutions of the right hemisphere, especially the frontal and occipital lobes. The brain weighs 720 grammes. Left hemisphere = 320 grammes; right hemisphere = 310 grammes; cerebellum, pons and medulla = 90 grammes, $8 \times 90 = 720$ grammes. The convolutional pattern is of normal complexity and the relative weight of the cerebellum, pons and medulla bears the normal index of 1-8, showing that the cerebral hemispheres are as regards weight not under-developed. It was observed, however, that the frontoparietal operculum at the anterior end of the Sylvian fissure is not closed, as if there were an arrest of development of the inferior frontal convolution. The substance of the hemispheres feels tough and indiarubber-like, especially on the surface. The cerebellum has not nearly so firm a consistence. The spinal cord with some of the lumbo-sacral nerves and spinal ganglia were removed. The cervical sympathetic and ganglia were removed.

Thorax.—There were pleural adhesions at the posterior border of the lungs on both sides. No fluid. The base of the left lung is solid with broncho-pneumonia, also part of the base of the right lung. On expression the organs exude muco-purulent matter from the small bronchi. The heart is very small, the substance paler than normal, all the valves are healthy. The aorta appears to be rather thinner than natural.

Abdomen.—The liver weighs 1 lb. 2 ozs., very pale, of about normal size, but of a pale olive yellow colour; it is firm in consistence, with smooth, sharp edges. The kidneys are pale, capsule non-adherent. The adrenals are pale and ochre-looking throughout. The pancreas is large, very firm and fibrous. Stomach and intestines beyond the walls being thin and pale, show no naked eye change. The testicles are of about normal size. Portions of the tissues of all these organs were taken for histological examination.

HISTOLOGICAL EXAMINATION.

Tissues hardened in formol Müller, sections cut in celloidin, stained with logwood and eosin.

Organs examined.—(1) heart; (2) liver; (3) pancreas; (4) spleen; (5) kidneys; (6) suprarenal; (7) sympathetic ganglion; (8) spinal cord; (9) cortex cerebri.

Heart.—There is a great excess of nuclei, as if a marked proliferation had occurred, and the sarcoplasm of the fibres was proportionally under-developed. The sarcoplasm is stained pink and shows no striæ, the nuclear proliferation is also seen in the connective tissue and the walls of the nutrient vessels.

Pancreas.—There is a marked infiltration of the interstitial tissue with leucocytes and young connective tissue cell proliferation of the supporting framework of the whole gland; this extends to the interlobular and interacinous tissues. In many places there are numbers of red blood corpuscles free in the spaces of the tissues, owing to capillary extravasations. The intensity of the inflammation and the amount of dense fibrous tissue varies in different situations. In some places the interlobular tissue consists mainly of an increase of dense fibrous tissue around thick-walled vessels, with some scattered blood corpuscles and leucocytes, the termination of a previous inflammatory condition. In other places the interlobular space is filled with leucocytes, evidence of an acute inflammatory process which here and there extends to the interacinous tissues and has even destroyed the secreting gland cells, leaving only the proliferated nuclei of the interacinous tissue and the nuclei of the basement membrane of the acini.

The secreting gland cells.—Under a low power these cells show a very marked difference in their staining reaction; whole lobules or acini are but faintly stained as compared with others which are moderately but unevenly stained. The former examined with an oil immersion 1.45 Zeiss apochrom. and 8 ocular show large swollen faintly stained nuclei (*vide* photomicro. v.). They appear to have little or no surrounding cytoplasm. In the less affected lobules, the nuclei are more deeply stained and surrounded with a little granular cytoplasm, while some have a fairly deeply stained substance; occasionally there are demilunes seen.

Testicle.—There is no lack of nuclei in the spermatid tubes, nor in the interstitial and surrounding substance. The organ appears to be normal.

Stomach pyloric end.—Only the cells at the base of the gland are stained with the basic dye, and these very imperfectly and only partially. This condition is more marked in the stomach than in the duodenum; the nuclei are swollen, clear, and faintly stained. At the base of the tubule some of the cytoplasm is deeply stained around the nucleus, which with the exception of the nucleolus, nuclear strands and nuclear membranes is only faintly stained. All the remainder of the cells of the tubular glands are faintly stained by the acid dye, a purplish pink.

Duodenum.—The same change is found with the exception that more cells take the basic dye at the base of the tubule, and many of the nuclei of the villi and tubular glands take the basic dye.

Spleen.—The organ shows some thickening of the capsule and increased thickness in the fibrous trabeculæ.

Liver.—The capsule is somewhat thickened ; around every portal canal there are evidences of a chronic inflammatory process, each vessel shows surrounding it, a layer of proliferated epithelioid cells and leucocytes. The liver cells are mostly distended with fat, but there is a marked nuclear proliferation and leucocyte accumulation.

Adrenals.—These glands show a similar inflammatory process.

Cortex cerebri.—Stained by Nissl method, sections of 5 μ thickness were cut in paraffin. The ganglion cells are seen clumped together, but they are better stained than in Case I. Although there is a great deficiency of the basophil substance, the cells are either stained throughout by a fine purple-coloured dust, or the cytoplasm is only faintly stained, the Nissl granules being absent in all cases, yet the shape of the cell is less altered, and in every cell the nucleus is visible, the nuclear membrane and nucleolus being fairly deeply stained. Sometimes around the nucleus can be seen a residuum of basophil substance ; the remainder of the cytoplasm in such instances is either only faintly stained or not stained at all. There is a considerable proliferation of the neuroglia cells and fibres when sections are stained by the appropriate methods. The Weigert fibres are seen especially around the vessels, and in the superficial part of the cortex, but they are *not nearly so abundant as in Case I.*

The spinal-ganglia and sympathetic ganglia were examined, and in both instances the cells showed the characteristic change of disappearance of the basophil substance, from the periphery of the neuron back towards the nucleus ; so that most of the cells in these situations showed a quantitative disappearance of the basophil substance in all stages. The last place in the cell in which it disappears, is the cytoplasm immediately surrounding the nucleus (*vide*, fig. 4, plate ii.). All the neurons, whether sympathetic or cerebrospinal, show this regressive phenomenon ; specimens of the spinal cord, medulla, pons and cerebellum were examined with similar results, the most advanced changes apparently affected structures of latest development, viz., the cortex-cerebri. The spinal ganglion shows, apparently, not only a change in the ganglion cells, but also a proliferation of the endothelial cells of the capsules.

Cortex examined by the Weigert hæmatoxylin method.—The sections of various parts of the cortex exhibited an almost complete disappearance of tangential fibres, a marked diminution of super-radial and inter-radial fibres. The radial fibres were abundant, but their stainable myelin sheaths were very attenuated. Not a few of the fibres presented a varicose appearance. A great

number of the ganglion cells appeared purple from the presence of a fine dust which was stained purple like the myelin. This is indicative of a fatty degenerative change. Both the cortex and cerebellum stained by the Weigert hæmatoxylin method show a picture of myelinated fibre, both as regards distribution and thickness of the myelin sheath, more like that which would be obtained from the brain of a child shortly after birth, than that of a child a year old.

The spinal cord stained by the same method showed far less degenerative atrophy of the fibres than did Case I. There is a naked eye sclerosis in the lateral columns, corresponding with the crossed pyramidal tracts, but there is no naked eye degeneration of the cerebellar tracts and posterior columns as in Case I. Moreover, the crossed pyramidal degeneration, although very extensive, is not absolutely complete, as in Case I. The spinal cord stained for glia exhibited a general pial, subpial and septal glia cell proliferation, and there was a great increase of glia cells in the grey matter. The anterior and posterior "roots" of the spinal cord in section show fairly normal bundles of myelinated fibres, which indicates that although profound changes have taken place in the cytoplasm of the anterior and posterior spinal ganglion cells; the axons are, nevertheless, capable of functioning. This fact, when taken in conjunction with the fact that Gordon Holmes has shown that the essential change is not (at least primarily) one of the fibrillary conducting substances, but of the basophil interfibrillary substance is of great importance in considering the pathology of this disease in its bio-chemical aspects. The chemical examination in these cases has been carried out by my assistant who has furnished me with the following report.

CHEMICAL EXAMINATION OF THE BRAIN IN TWO CASES OF
AMAUROTIC IDIOCY, BY SIDNEY A. MANN.

The methods for the quantitative analysis of the brain described by Koch (*American Journal of Physiology*, June, 1904), and amended in his more recent publications, were used in this examination. The following is a brief account of the method of separation of the various constituents:—

The grey or white matter is extracted several times with alcohol and ether.

(1) *Portion soluble in alcohol and ether.*—This contains the cerebins, lecithins, sulphur compound and cholesterin. The alcohol and ether are evaporated, and the residue made into an emulsion with water; this is acidified with hydrochloric acid, a few cc.s of chloroform added, and the whole made up to known volume and well shaken. After standing for a few days the *lipoid precipitate* separates out, leaving a clear solution of the

inorganic salts and extractives (organic compounds soluble in water). In the lipoid precipitate the lecithans and sulphur compounds were estimated, and in the clear filtrate the inorganic salts and extractives.

(2) *Portion insoluble in alcohol and ether.*—This is extracted several times with chloroform water, in order to remove the inorganic salts and extractives, which are estimated and added to the quantity determined above. In the residue the amount of nucleo-proteid is determined, and by difference the quantity of simple-proteid (neurokeratin, &c.), obtained.

The following table shows the percentage composition of the white and grey matter in each case, compared with the figures given for a normal brain by Koch (*Cf.* p. 340). It is unfortunate that analyses of a normal brain of a child of similar age are not available for comparison. However, in the absence of such data, the figures taken for the normal brain represent the average percentage composition of the grey matter, and the corpus callosum of the white matter of an adult brain.

Case I.—The material for analysis was taken from the temporal lobe.

Grey matter: The grey matter was leather-like in consistence, but the amount of moisture was found to be in excess of the normal. The notable feature of these analyses, however, is the excess of simple proteid (presumably an excess of neuro-keratin, and the marked diminution in the amount of nucleo-proteid). The *lipoid* constituents, lecithans and sulphur compound (p. 340) are diminished.

TABLE I.—SHOWING PERCENTAGE COMPOSITION OF THE BRAIN IN THE AMAUROTIC IDIOCY CASES COMPARED WITH A NORMAL BRAIN.

	GREY MATTER			Normal	WHITE MATTER		Normal	
	Amaurotic idiocy				Amaurotic idiocy			
	Case I.	Case II.			Case I.	Case II.		
Water ..	85.34	(a) 82.65	(b) 83.9	81.2	87.5	79.71	69.6	Cerebrins and cholesterin not estimated in either case.
Simple proteid	5.68	5.32	5.31	4.25	3.83	4.71	4.4	
Nucleo-proteid	1.17	1.93	1.58	4.45	1.82	3.04	3.8	
Lecithans ..	2.25	3.33	3.45	4.0	2.53	4.51	7.5	
Lipoid sulphur compound	0.76	0.23	0.23	1.0	0.59	0.95	2.3	
Extractives ..	1.81	1.72	1.98	2.1	2.39	2.11	1.4	
Inorganic salts	0.82	0.96	0.83	1.2	0.75	0.55	0.8	

White matter: In appearance the white matter was of a thick creamy character, and the percentage of water was found to be exceedingly high. The above analyses show a diminution of, all

the solid constituents except the inorganic salts and extractives, the former remain about normal, while the latter show a marked increase; this would be accounted for by the watery condition of the white matter. The total solids, however, have diminished by more than one half, and the above results do not show the real comparative amounts of the various solid constituents present. Table II. is therefore given showing the various solid constituents calculated in percentages of the total solids.

Case II.—The brain presented a normal appearance, but on section it was found that the grey matter consisted of a thin "leathery" film on the external surface with the remainder of the grey matter of slightly below normal consistency. The white matter for the greater part was hard and firm, but at its junction with the grey matter, and also at the inner portions, it was soft, and in places of a very thick creamy character. The condition of the white matter rendered the determination of an accurate figure for the water content a difficult matter, and too much significance should not be attached to the result given, which is, in my opinion, too high. Thus the brain differed from Case I. in the change not being so advanced, in which case the grey matter *throughout* was hard and firm, and the white matter of a creamy consistency. The nature of the cortex rendered the collecting of the material a very difficult matter, and the taking up of some of the white matter could not be avoided.

In view of this fact, two 12 gramme samples of the grey matter were collected: (a) from the motor area; (b) from the prefrontal area; the results, however, do not show any wide discrepancy.

Grey matter: As in Case I., but to a less degree, the simple proteid is increased, and the nucleo-proteid diminished in amount. The lipid constituents are below normal, especially in the case of the sulphur compound; the rest of the analyses are practically normal.

White matter: Altogether the phosphorus and sulphur content of the white matter is low, the lecithans are considerably diminished, and the nucleo-proteid slightly so; the lipid sulphur compound is also decreased in amount. The extractives and the simple proteid are increased, but as will be seen in the following table the increase in simple proteid is much less than in the white matter of Case I.

Grey matter: Viewing the results calculated in this manner it is observed that the simple proteid in both cases is increased in amount, and the nucleo-proteid diminished; in each instance, however, the departure from the normal is not so great in Case II. The change in Case II. may possibly be exaggerated by the mode of collecting the material; the grey matter had to be taken from the external surface of the cortex in order to avoid contamination

with the white matter, whereby the superficial layer of leathery cortex was always taken in, whereas in Case I. the grey matter was hardened throughout and could easily be rendered free from the creamy white matter.

TABLE II.—SHOWING THE SOLID CONSTITUENTS CALCULATED IN PERCENTAGES OF THE TOTAL SOLIDS.

	GREY MATTER			Normal	WHITE MATTER		Normal	
	Amaurotic idiocy				Amaurotic idiocy			
	Case I.	Case II.			Case I.	Case II.		
Simple proteid	38.74	(a) 30.6	(b) 32.9	22.6	30.6	17.1	14.4	Cerebrins and cholesterin not estimated in either case.
Nucleo-proteid	8.00	11.1	9.8	25.6	14.5	11.1	12.4	
Lecithans ..	15.38	19.2	21.4	21.2	20.2	16.4	24.6	
Lipoid sulphur compound..	5.22	1.3	1.4	5.3	4.7	3.4	7.5	
Extractives ..	12.35	9.9	12.3	11.1	19.1	7.7	4.6	
Inorganic salts	5.63	5.5	5.1	6.3	6.0	2.0	2.6	

The lecithans are diminished in Case I. but normal in Case II., but the lipoid sulphur compound is normal in Case I. and diminished in Case II. The extractives and inorganic salts give practically normal analyses.

White matter: The total solids in Case I. were diminished by more than one half, whereas in Case II. they were much nearer the normal. The simple proteids in the former case are largely increased with the nucleo-proteid remaining about normal, but it will be observed that *the percentage of total proteids of the total solids is nearly twice as much as the normal*. The white matter in this case shows a diminution of the lipid constituents, and a large increase in the amount of extractives and inorganic salts.

Case II. shows no great departure from the normal in the amount of simple proteid and nucleo proteid present; the lecithans and sulphur compound, however, show a diminution, more so even than in Case I., while the extractives are somewhat increased. The analyses in this case certainly approach those of a normal brain.

Summary.—In both cases, but to a less degree in Case II., there is an excess of simple proteid with a corresponding decrease of nucleo-proteid, changes so marked that they may be regarded as outside the limits of chemical error or unfair comparison.

The water content is increased in both cases, but the change is most marked in Case I.; however, the brains of young children usually contain more water than adult brains, and the increase noted in the cases analysed may be partially normal.

The variability of the analyses of the extractives and inorganic salts, is no doubt controlled by the amount of water present.

The lecithans show a variable diminution, a result which may be of significance, and the decrease of the lipoid sulphur compound, more marked in Case II., is of interest, but the results should be confirmed on larger samples before any conclusions may be drawn.

The only facts which appear to be outside the limits of error are two, viz. : (1) the decrease of nucleo-proteid, which may be associated with the disappearance of the Nissl substance in the neurons ; and (2) the increase of simple proteids, which may be correlated with the increase of glia fibrils.

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Conclusions.—The essential histological feature of this disease is a progressive loss of the Nissl substance of all the neurons in the body. The mode in which this substance disappears is progressively from the periphery of the neuron towards the nucleus in the centre of the cell ; it may therefore be assumed that the Nissl substance is a derivative of nuclear bio-chemical interaction on the cell protoplasm and its lymph environment. Reasons have been given to show that histo-chemical observations support the view that this substance is a nucleo-proteid. The results of the chemical analyses of these two brains, when correlated with the histological observations, strongly support the view that this interfibrillary basophil staining substance which forms the Nissl pattern of the normal neurons is a nucleo-proteid. Gordon Holmes has shown that the neuro-fibrils may persist and the axons retain their myelin sheath when the Nissl substance has disappeared from the cell.

The inference is, then, that the profound affection in the physiological functions of the central nervous system which characterises this disease may be especially associated with a bio-chemical change in the metabolism of the nucleus. The cause of this regressive metabolic metamorphosis may be an inherent lack of specific energy, racial or familial, of the neurons and possibly some hitherto undiscovered bio-chemical alteration of the blood or lymph. The existence of the neuro-fibrils, which may be regarded as the conductile structure of the neurons, which clinical facts tended to

show had ceased to function, would support the view either that the Nissl substance which had disappeared was itself an important agent in neural function, or that it was an antecedent of a substance at the synapses. The increase of the neuroglia fibril substance to an abnormal degree in Case I. so that the brain weighed heavier than that of a normal adult, accounts for the large amount of simple proteid and the great diminution of nucleo-proteid.

BIBLIOGRAPHY.

- SCOTT. *Brain*, Autumn and Winter Number, 1905, p. 507.
 FREY, E. *Neurologisches Centralblatt*, s. 836.
 HIRSCH, W. *Journal for Nervous and Mental Diseases*, 1898, p. 538.
 HOLMES, GORDON. "Study of Amaurotic Family Idiocy," *Brain*, Part cxiv., 1906.
 KINGDON AND RUSSELL. *Medico-Chirurg. Transactions*, 1897, vol. lxxx., p. 87.
 PETERSON, F. *Journal for Nervous and Mental Diseases*, 1898, p. 529.
 SACHS, B. *Ibid.*, 1887, p. 541; *Ibid.*, 1892; *Ibid.*, 1903.
 SACHS, B. *Deutsche Med. Wochenschrift*, 1903, s. 494.
 SCHAFFER, K. *Wiener Klinische Rundschau*, 1902; *Neurologisches Centralblatt*, 1906, s. 51.
 SPILLER, W. G. *American Journal for Medical Science*, 1905.

ADDENDUM.

Since the above paper has been in print, the brain of a child aged 1 year 11 months has been obtained, through the kindness of Dr. A. N. Leathem. With a view of controlling the comparison of the amaurotic idiocy cases with a normal adult brain, I instructed my assistant, Mr. Sidney Mann, to proceed with the chemical analysis thereof. The full results will be published at a later date, but the nucleo-proteid and simple proteid estimations have been made, and they do not appreciably alter the conclusions drawn from the former comparison. The figures are as follows :—

	PERCENTAGE COMPOSITION			PERCENTAGE OF TOTAL SOLIDS	
	Grey matter	White matter		Grey matter	White matter
Moisture ..	84.49 %	76.45 %	..	—	—
Simple proteid	5.20 %	4.32 %	..	33.5 %	18.3 %
Nucleo-proteid	2.57 %	3.37 %	..	16.5 %	14.3 %

It will be observed that, compared with Koch's figures for a normal adult brain, the nucleo-proteid is practically the same, while the simple proteid shows an increase; but with the amaurotic idiocy cases, the increase of simple proteid and diminution of nucleo-proteid noted in Case I. is still very marked; with Case II., the nucleo-proteid still shows a diminution, but the simple proteid is practically normal.

CARBON MONOXIDE AND NICKEL CARBONYL POISONING.

THE SYSTEMATIC EXAMINATION OF THE CENTRAL
NERVOUS SYSTEM IN A CASE OF POISONING BY ILLU-
MINATING GAS, AND TWO FATAL CASES OF POISONING
OCCURRING IN THE CARBONYL OF NICKEL WORKS.

BY F. W. MOTT, M.D., F.R.S.

SUMMARY.

- (I.) Introduction.
- (II.) The increase of number of deaths from carbon monoxide poisoning since admixture of carburetted water gas has become general in the supply of illuminating gas.
- (III.) The symptoms of acute and chronic carbon monoxide poisoning.
- (IV.) Experiments with carbon monoxide gas and the vapour of nickel and iron carbonyl on animals. Comparison of the results with fatal cases in the human subject.
- (V.) The correlation of the lesions found in cases of carbon monoxide poisoning and the symptoms manifested during life in fatal cases and in cases which recover but with permanent damage of the nervous system.
- (VI.) The possibility that certain little understood or undiagnosed morbid conditions which terminate fatally in some instances may be the result of acute or chronic carbon monoxide poisoning.
- (VII.)—(i.) Report of a case of suicide of a mother and homicide of her two children. The mother lived four days and the examination of the nervous system is recorded. (ii.) Report on the examination of the brain in two fatal cases from the Nickel Carbonyl Works.

I.—INTRODUCTION.

I was requested by Dr. Ludwig Mond to examine and report upon the brains of two workmen who had died at the Nickel Carbonyl Works. By his kind permission I have been allowed to publish the reports which I furnished. Since writing these reports I have had the opportunity of studying during life and *post mortem* a fatal case of carbon monoxide poisoning, the result of inhalation of illuminating gas. This case presents many interesting points medicolegally; it is also of interest when the pathological changes are compared with those found in the two cases from the Nickel Carbonyl Works. The *post-mortem* findings in this case of suicide by illuminating gas four days after its inhalation corresponds very closely with the *post-mortem* naked eye and histological findings in the brains of the two cases of poisoning occurring at the Nickel Carbonyl Works, Clydach. In my report I ventured to suggest that these workmen had died of carbon monoxide poisoning. There are, however, reasons why this should not be so, and the fact that similar changes were found in the brain of the person dying of poisoning by illuminating gas does not *prove* that my supposition was correct, although it tends to show either that the workmen died from the effect of carbon monoxide unsuspectingly inhaled, or that nickel carbonyl vapour which they might also have inhaled, produces changes in the brain like those of carbon monoxide poisoning.

Cases of poisoning by carbon monoxide may be accidental, suicidal, or homicidal, and the two latter combined, as in the case reported. In France four-fifths of the suicides are caused by carbon monoxide poisoning. This gas may be produced in houses by defective combustion in various forms of heating apparatus, in particular by movable stoves, charcoal braziers and slow combustion stoves. I once saw two children brought to the hospital dead; their lips and cheeks were cherry red and it was only after listening to the heart that we could believe they were dead. The history was that they had been shut in a room with a large pile of old rags which had caught fire and slowly smouldered away.

Men frequently are found dead in lime kilns, and near coke ovens poisoned by this gas.

Since however carburetted water gas has been purveyed as an admixture to illuminating gas the danger to life of defective gas fittings, geysers and gas stoves, as well as leaking pipes or mains in the soil has greatly increased and the number of accidental deaths and suicides have multiplied enormously as the subjoined statement of an eminent authority, Professor Glaister of Glasgow shows. It is an easy mode of death and as in the case reported it can be carried out without causing any suspicion. Carbon monoxide is the poisonous constituent of mine air when explosions occur, also of the gas of blast furnaces and, as is mentioned later, carbon monoxide poisoning may occur in many other occupations, it is therefore a matter of importance in INDUSTRIAL PATHOLOGY. I am publishing the observations of these three cases, at the suggestion of Dr. Haldane who has had so much practical experience in carbon monoxide poisoning and whose investigations have been attended with such valuable practical results.

I am indebted to Professor Glaister of Glasgow for the following statement respecting the dangers arising from the supply of carburetted water gas as an admixture to illuminating gas. Carburetted water gas is made by passing water gas over a large superficies of heated refractory material charged with oils rich in hydrocarbons, the result being that the more volatile hydrocarbons are vapourised or rendered gaseous and become mixed with the water gas. The volatilised hydrocarbons thus incorporated are mainly benzine and benzine congeners, and impart to the product an odour similar to the characteristic odour of coal gas. The difference between olefiant or coal gas and producer gas, water gas, and carburetted water gas lies in the relatively much higher proportional amounts of carbon monoxide which these last-named contain. This difference is of great importance from the public health point of view with relation to the increased dangers to health from small leakages from pipes in dwellings, and to the risks of greater fatality from large leakages.

II.—Evidence as to fatal cases of coal gas poisoning was placed before a Departmental Committee of the Home Office on water gas in 1898-99.

In England and Wales, for a population equal in number to that of London in 1896 the number of fatal accidental cases of gas poisoning, in places where coal gas alone was used, was 3 only. In 88 American cities supplied with coal gas only, the number of deaths was the same. In Boston, which is supplied with 90 per cent. of carburetted water gas, the deaths numbered 390; in Brooklyn with 97 per cent., 120; in Chicago, with 100 per cent., 155, and in San Francisco, with about 70 per cent., 270.

In other cities of the United States, after installation of carburetted water-gas, similar increases in the death-toll have been recorded. For example, in the combined populations of New York, Brooklyn and Baltimore amounting to about 2 millions, for the thirteen years prior to the use of water-gas (introduced therein in 1880) there had only been registered sixteen cases of gas poisoning, whereas during the seven and a half years thereafter, the number of cases had risen to 120.

From a careful statistical consideration of the Parliamentary Returns of Gas Undertakings for 1904, Professor Glaister finds that of 454 private company undertakings in England and Wales, 68 of these, or 15 per cent. of the whole in this class, supply some measure of admixed carburetted water gas in their illuminating gas; in Ireland, of 10 private company undertakings 3 supply some admixture and that in Scotland, of 5 private company undertakings none supply carburetted gas.

From the Returns for 1905 of Local Authorities who are gas undertakers, he finds that in England and Wales, of 208 local authorities, 28 of them, or 13·5 per cent., of this class of producers supply admixtures of the gas; in Scotland, of 46 local authorities 3 only supply admixtures or 6·5 per cent. of producers, and in Ireland, of eleven authorities, only one sends admixture of carburetted gas.

The percentages of admixtures actually purveyed by the private gas companies in England and Wales vary con-

siderably in amount. They range from 60·7 per cent. in Southgate, down to 3 per cent. in Waltham, Southend, Liverpool, Tottenham, Norwich, Bath, and others supply between 50 and 60 per cent. admixtures. Folkestone, Wandsworth, Harrow, Hornsey, Croydon, Hastings and others, between 40 and 50 per cent. ; Falmouth, Gravesend, London (Commercial and South Suburban), Epsom, Brighton, Hull Station and others, between 30 and 40 per cent., and Durham, Hartlepool, Swansea, Newcastle, Eastbourne, Scarborough, York and many others between 20 and 30 per cent.

The percentage of admixtures purveyed by municipal gas producers in England and Wales vary from 56 per cent. in Southport, the highest, to 12 per cent. in Leicester, the lowest. Of these producers Oldham supplies between 40 and 50 per cent.; Burnley, Manchester, Lincoln and Coventry, between 30 and 40 per cent.; Stockport, Carlisle, Stockton-on-Tees, Blackburn, Birmingham, Leeds, and several others between 20 and 30 per cent.; the rest supplying less than 20 per cent. admixture.

Of the three municipal authorities in Scotland who supply admixtures, Dundee uses 25 per cent. and Edinburgh and Leith 4·23 per cent. Glasgow does not supply any admixture of carburetted gas in its supply. The total output of carburetted gas by private and municipal gas undertakers is on the increase.

In 1878 the number of private undertakers in the United Kingdom was 439, and the total output of this gas was a little over 5 millions of cubic feet. In 1904, the number of undertakings having only increased by thirty, the total output of this gas had risen to $13\frac{1}{2}$ millions of cubic feet.

In 1898, the number of municipal gas undertakers was 222, and the total output of this gas was $2\frac{1}{4}$ millions of cubic feet, whereas in 1904-5, the number of undertakings having risen to 265, the output had risen to over 5 millions of cubic feet. These figures illustrate the increased risks to users of gas by reason of the larger percentage amounts of carbon monoxide which the supplied products contain and it is

not surprising to learn that in cities in which carburetted gas is supplied in large admixture, increased fatalities have to be recorded, as, for example, in Liverpool and Belfast.

Professor Glaister, in his "Text-book of Medical Jurisprudence, Toxicology, and Public Health," pp. 455 *et seq.*, cites the following examples of Coal-gas Poisoning:—

"January, 1895.—Underground or cellar dwelling occupied by family consisting of father, mother and five children, the children being aged 12 years downwards. There was *no* gas supply to the apartment, which was a large single apartment. Owing to strong smell of gas and the non-appearance of members of the family door was burst open by police. Mother and all the children were found to be dead, the father being still alive but deeply comatose. He also died later in the Royal Infirmary to which he was removed. There were no rosy red colourations of the skin of any of the bodies.

"*Cause of mishap.*—Bursting of a gas sub-main in an adjoining lane and percolation of gas through earth into apartment.

"(2) Six days later, January 18, called to deal with another series of coal-gas poisoning involving five persons, happily, however, without loss of life.

"(3) Case in Western Infirmary, under the late Dr. Finlayson. I was asked to see the patient with him. Took samples of blood in capillary tubes, and on micro-spectroscopic examination found typical spectrum of carboxy-hæmoglobin."

I may add that it is a constant occurrence now to read in the London papers of people poisoned by the escape of illuminating gas in dwellings; only recently five persons were found by the police, three of whom were dead. The cause in this instance was an indiarubber junction which had become perished.

*Other Cases of Carbon Monoxide Poisoning investigated
by Professor Glaister.*

(1) *From lime-kilns in proximity to inhabited dwellings.*

November 30, 1899.—In an inhabited street in Glasgow is a lime-burning works, consisting of three kilns, one of

which, at least, came within a few inches of the rough brick gable end of the tenement, the division being filled in back and front with cement, thus enclosing a space covering the outer wall of the kiln and the wall of the tenement.

During the night of November 30, 1899, the members of a family living on the ground floor apartments next the gable in question, after retiral to bed, were seized with faintness, sickness and vomiting, which was attributed to a disagreeable pungent smell in the apartments. The father, who had just then returned from work, found his family in this condition and had them removed to the house of a neighbour, where they quickly recovered. The family occupying the apartments on the flat immediately above, however, did not appear next morning. Alarm was raised and the house was entered by the police by a window. A woman and her two children were found dead in the bed in the kitchen, and a male lodger in a deep state of coma, but still alive, in the room apartment. The lodger was immediately removed to the infirmary, where, after treatment, and particularly after venesection and saline injections, he recovered. Having made *post-mortem* examinations for the Crown of the bodies of the woman and children, aged 4 years and $1\frac{7}{8}$ years, respectively, I found the skin of each of their bodies bearing marks of rosy red colouration, and, on dissection, an arterial hue of the blood of the body generally. By spectroscopic examination the presence of carbon monoxide hæmoglobin was easily detected. In the case of the woman the degree of saturation was 70 per cent.: she was advanced eight months in pregnancy of twin children.

(2) A man died in a public works in Glasgow under peculiar circumstances. He was set to work to clear off "scale," the inside plates of a retort. He began work about 6.30 a.m.; at the breakfast hour, notwithstanding he was called on different occasions, he did not emerge. On examination of the interior he was found to be dead. On making a *post-mortem* examination for the Crown, I found his body to be markedly rosy-coloured, his blood to be arterial hued, and on spectroscopic examination, the

spectrum of carbon monoxide hæmoglobin; the degree of saturation being about 75 per cent. This retort was part of a water gas plant, although it was alleged at the time the retort was not in use.

(3) Several deaths from carbon monoxide of tramps lying down to sleep on smouldering coal refuse heaps, doubtless attracted by the warmth.

III.—THE SYMPTOMS OF ACUTE AND CHRONIC CARBON MONOXIDE POISONING.

"The symptoms of carbon monoxide poisoning are essentially the same as those produced by air deficient in oxygen, and vary according to the degree of saturation of the hæmoglobin with carbon monoxide. With 20 per cent. saturation the only symptom is a slight tendency to dizziness and shortness of breath on exertion. As the saturation increases, however, the symptoms of want of oxygen become more and more pronounced until at 50 per cent. saturation it is scarcely possible to stand, and even slight exertion causes temporary loss of consciousness. The onset of the symptoms is *very insidious, there being only slight shortness of breath and palpitation but hardly any discomfort*; and the senses, power of judgment and of movement, are commonly much impaired before the person is conscious of anything being wrong. In some cases there is much excitement, but often there is simple drowsiness and stupidity."—HALDANE.

The symptoms are therefore not unlike alcoholic poisoning in some respects, no doubt varying according to individual temperament. It is a curious fact, also, that in reading the history of cases one finds that in carbon monoxide poisoning, as in alcoholic poisoning, sudden exposure to the cool fresh air produces sometimes an increase of the symptoms. In view of the change in certain nuclei of the medulla (cardio respiratory) which I found, it is of interest to note that death frequently immediately follows muscular exertion, as in attempts to escape rapidly up ladders, inclines, &c. In fatal cases 80 per cent. of the hæmoglobin is saturated with carbon monoxide, according

to Haldane. Persons who have been long exposed to carbon monoxide, rescued alive but still unconscious, die later on in consequence of damage to the tissues. In my case it is clearly shown by the clinical symptoms and the *post-mortem* findings, macroscopic and microscopic, that this damage falls especially upon the nervous system.

It is with considerable hesitation that I venture to suggest, in opposition to the eminent authority of Dr. Haldane, that carbon monoxide inhalation, when it proves fatal produces death only partly by the anoxæmia; otherwise the woman who was found alive but unconscious, should have recovered with artificial respiration and inhalation of oxygen. The great majority of the red corpuscles in the blood showed a basophil reaction; instead of taking the eosin stain, they take the methylene blue, thus indicating an abnormal reaction. I found the same appearances presented by the corpuscles in the rabbits poisoned by Dr. Oliver with nickel carbonyl. The carbon monoxide may alter the elasticity of the corpuscles and their physical properties in some way so that in certain regions where other factors exist which tend to interfere with the circulation through the capillaries, a tendency to stasis is set up. Moreover the plasma must always contain carbon monoxide during the process of association and dissociation of the carbon monoxide from the hæmoglobin which, according to Haldane, gradually takes place. The question arises does this carbon monoxide behave entirely as an inert gas. In the two cases from the nickel carbonyl works, there was evidence of endothelial irritation with mitosis and rupture of the walls of capillaries and small vessels; some of the hæmorrhages were of older date, and by the fact that there was well-marked Marchi degeneration in the white matter of the whole of the central nervous system, they probably corresponded to the first attack of the patient; for it is related that Case II. suffered with migraine, headache and pain in his stomach for a day or two before he gave up his work. It is probable that a number of factors conspired together to produce the extraordinary hæmorrhagic condition found, viz.: (1) returning to work and

receiving a fresh dose of the poison on top of the previous dose; (2) the pneumonia which set in and which might be due to the irritation of the nickel or carbon monoxide, for it is not certain whether it was carbon monoxide or nickel carbonyl that caused the pneumonia. In my case the patient developed pneumonia before death, but signs of the cerebral hæmorrhages occurred before the pneumonia could have so altered the blood that it could lead to thrombotic occlusion. Doubtless the toxic condition of the blood, the result of the infection, increases its fibrinogenous character, but this alone never produces this hæmorrhagic condition of the brain, although it aggravates, without doubt, the condition set up by the carbon monoxide poisoning.

By Marchi staining, the small vessels showed that the endothelial cells in the case of carbon monoxide poisoning had undergone fatty degeneration, *vide* fig. 6, and this was probably the result of the carbon monoxide poisoning. Why should the hæmorrhagic condition be found in the white matter of the brain? It must be for some anatomical reason. The portions of the brain where the hæmorrhages are especially found are supplied by the perforating arteries, long delicate-walled *terminal* arteries, surrounded by a wide lymphatic sheath containing cerebro-spinal fluid. These arteries break up into a network of capillaries around bundles of nerve fibres. In carbon monoxide poisoning there is always a tendency to heart failure and fatty degeneration. *A number of conditions*, therefore, tend to stasis and rupture of these vessels, viz. :—

- (1) Weak heart acting against gravity.
- (2) Terminal distribution of these arteries.
- (3) Delicate walls of the arteries and arterioles, the endothelium of which microscopically is seen to be affected with fatty degeneration.
- (4) Narrow lumen of the capillaries forming the network and resistance to the flow through them.
- (5) Altered state of the blood corpuscles and plasma, by which there is a tendency to stasis, *vide* statement of Dr. Le Neve Foster, p. 260, and experiments of Lancereaux.

IV.—EXPERIMENTS WITH CARBON MONOXIDE AND NICKEL CARBONYL UPON ANIMALS.

Is there any evidence, experimental or otherwise, which supports the idea that carbon monoxide not only causes lesions by deprivation of the tissues of oxygen, by turning out the hæmoglobin? That is to say, does it by virtue of its presence in the plasma exert a toxic influence on the tissues?

Lancereaux has demonstrated in the transparent wing of the bat, an accumulation of blood in the small vessels when the animal is placed under the influence of carbon monoxide. According to Linossier animals died sooner and did not present the same symptoms when placed in an atmosphere of carbon monoxide, as when asphyxia was induced by placing them in an atmosphere of nitrogen. He has also shown that snails, which have no hæmoglobin, when placed in an atmosphere of hydrogen or nitrogen containing the same proportion of oxygen as in a mixture of carbon monoxide and oxygen, died much sooner in the latter. Lamie states that frogs can live three and a half hours in an atmosphere of nitrogen, but only one and a half hours in an atmosphere of carbon monoxide.

It is asserted that muscle can take up carbon monoxide independently of blood and give the spectrum.

Lancereaux considers that the red blood corpuscles perish under the influence of carbon monoxide, that these block the blood vessels and lead to thrombus formation. Pœlchen came to the conclusion that carbon monoxide poisoning produces a disease of particular vessels of the brain and of the tissue territories supplied by them. He considers that the disease is a primary affection of the arterial wall, which leads to secondary necrobiosis of the brain tissue.

Dr. Haldane's position is, however, an extremely strong one, as he has shown that all the symptoms, immediate and secondary, of carbon monoxide poisoning can be referred to want of oxygen. The most direct evidence he offers is that if animals are placed in oxygen at high pressure (1 to 2 atmospheres), and carbon monoxide then driven in on the

top of the oxygen they continue to live, although their blood and tissues are saturated with carbon monoxide and the amount present in the tissues is 200 or 300 times as much as would prove fatal if the animals were in air. They get from the high pressure oxygen enough of oxygen in *simple solution* in the arterial blood to supply the tissues with oxygen, and the carbon monoxide therefore does no harm. This experiment, which Haldane did on mice and reported in the *Journal of Physiol.*, vol. xviii., p. 211, and vol. xxi., p. 161, I am informed by Dr. Haldane has been repeated by Mosso with a large apparatus on monkeys, and with exactly the same result. Haldane has kept cockroaches for a fortnight in a mixture of 80 per cent. carbon monoxide and 20 per cent. oxygen without harm, and these experiments therefore disprove the experiments recorded by the French observers.

Dr. Haldane in a letter to me says that he has never doubted that the brain and often the heart, and probably other organs, are *damaged* by the want of oxygen, and he has called my attention to the fact that in his "Report on the Causes of Death in Colliery Explosions," p. 18, and in the Appendix to it by Dr. Lyttle, similar secondary symptoms to carbon monoxide poisoning are produced by temporary asphyxia by simple want of oxygen.

V.—EXPERIMENTS WITH CARBON MONOXIDE GAS, OR THE VAPOUR OF NICKEL AND IRON CARBONYL ON ANIMALS
COMPARISON OF THE RESULTS WITH FATAL CASES IN THE HUMAN SUBJECT.

Numerous experiments have been made upon small warm-blooded animals, and the mouse has been used as a valuable test (Haldane's) in the mines. I have examined the brains of animals poisoned with carbon monoxide, with coal gas, and with the vapour of nickel carbonyl and iron carbonyl, the brains having been forwarded to me by Dr. F. T. Oliver. The animals have generally died within thirty-six hours of the first inhalation, but I have found no such naked eye hæmorrhages in the white matter of the brain as I have found in the human cases reported here. There

have been numbers of microscopic hæmorrhages, however, in the pons and medulla as are represented in the accompanying figures, and chromolytic changes in the ganglion cells in the neighbourhood of these hæmorrhages.

The brain of a rabbit that survived three days after exposure to nickel carbonyl vapour exhibited, especially in

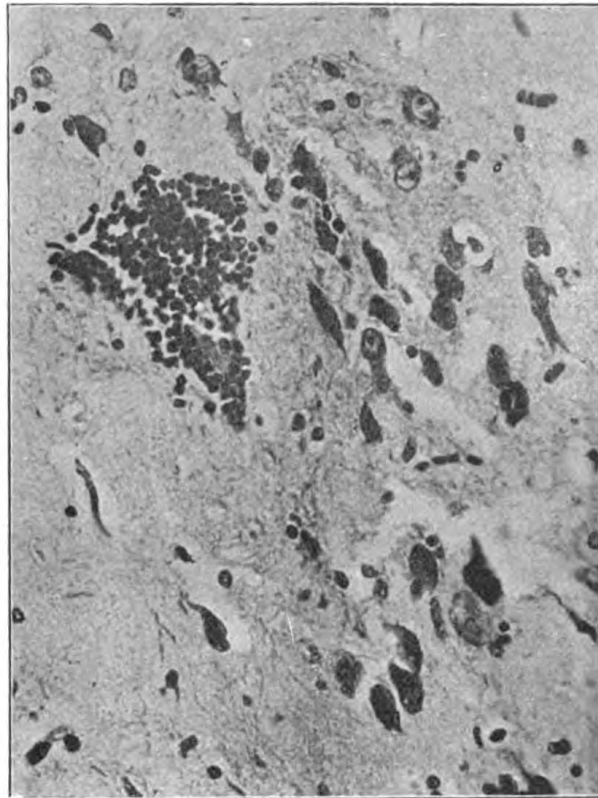


FIG. 1.—MICROSCOPIC HÆMORRHAGE IN THE MEDULLA OF RABBIT POISONED WITH NICKEL CARBONYL. Diffuse staining of ganglion cells.

the medulla oblongata, engorgement of vessels and hæmorrhages. Transections of the vessels showed, when stained with polychrome and eosin, a similar appearance of the corpuscles to that observed in the case of human carbon monoxide poisoning, viz., a large and variable number of the corpuscles took the basophil stain and appeared blue; in some vessels the whole of the corpuscles appeared blue, and the surrounding serum was stained pink. I en-

deavoured to reproduce this by passing coal gas through blood in a tube, but did not succeed. This supports Lancereaux in his opinion that the protoplasm of the corpuscles undergoes a change in fatal cases of carbon monoxide poisoning.

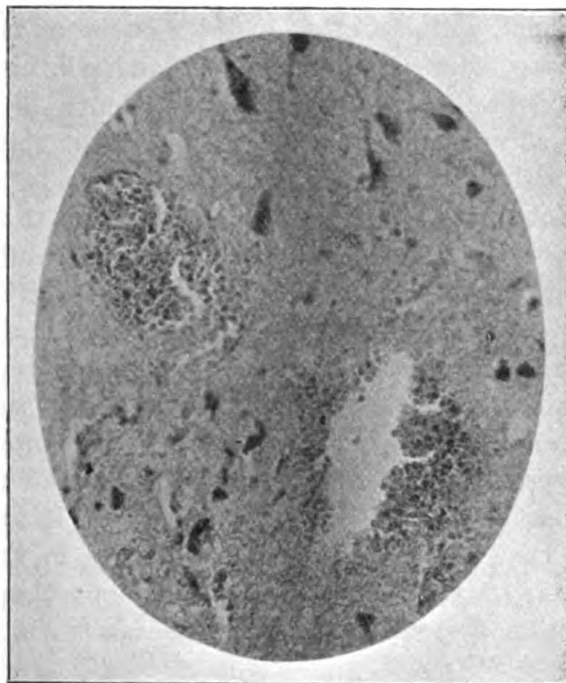


FIG. 2.—MEDULLA OF RABBIT WITH TWO HÆMORRHAGES. Nickel carbonyl poisoning.

In the sections of this animal's brain it appeared that there was commencing endothelial mitosis and commencing glia cell proliferation; a similar evidence of the irritant action of the poison was noticed in the human cases.

V.—THE CORRELATION OF THE LESIONS FOUND IN CARBON MONOXIDE POISONING, AND THE NERVOUS SYMPTOMS MANIFESTED IN FATAL CASES, AND IN PATIENTS WHO RECOVER, BUT WHOSE NERVOUS SYSTEMS ARE PERMANENTLY DAMAGED.

Before considering the above subjects, it will be well to give some facts relating to the effects of carbon monoxide poisoning, as narrated by intelligent persons who have

recovered. The most valuable and interesting are the detailed statements of Dr. C. Le Neve Foster and his associates.

It is of interest to note that while in some of the men there were disturbances of consciousness, in none was there loss of consciousness; this indicates a persistence of the functional activity of the grey matter of the cortex. The vomiting, faintness and palpitations point to anæmia of the medulla oblongata. The persistence of headache continued at intervals for some time after the accident, may also be due to an effect similar to anæmia.

The statement of Dr. Le Neve Foster, that he had absorbed enough poison to paralyse him and dull his feelings, but at the same time his reason had not left him, may be accounted for by the greater disturbance and tendency to stasis in the circulation of the arteries supplying the stem of the brain in which is contained the afferent sensory and efferent motor system; a stasis which we know in fatal cases may result in extensive and wide-spread rupture of small vessels and attendant hæmorrhages. It is probable, therefore, that the circulatory disturbances in the association systems of the cortex are less evident than those in the projection systems, even in those cases which are not fatal.

The Investigation of Mine Air. Sir C. Le Neve Foster, and Dr. J. S. Haldane.

Dr. C. Le Neve Foster in statements (made to the Home Secretary) concerning the sensations, symptoms, and after-effects of carbon monoxide poisoning, relates his own experiences while as Chief Inspector of Mines he was investigating the effect of carbon monoxide in connection with an underground fire at Snaefell Lead Mine; the physical and mental effect on four other gentlemen who descended the mine are recorded.

The notes he made at the time "afford ample confirmation of the effect produced by carbon monoxide poisoning of causing reiteration. I wrote the same words over and over again unnecessarily. The condition I was in was rather curious. I had absorbed enough of the poison to paralyse me to a certain extent and dull my feelings, but at the same time my reason had not left me.

"Mr. Williams, on the other hand, and Captain Reddcliffe, though not absolutely unconscious, did not recognise the lapse of time for they thought that only about ten minutes elapsed between my calling out 'all up at once,' and their arrival at the surface. In reality nearly two hours had gone by." Numbness of the fingers to such an extent that he had unconsciously burnt his wrist and hand with the candle. On returning to the air he had a feeling of exhilaration, was in full possession of his senses and able to walk, and an attempt was made by Dr. Miller to withdraw blood from a vein in the arm made turgid by a bandage, *but no blood could be drawn*. Mr. Williams was tried in the same way without success (these facts seem to my mind to indicate universal viscosity of the blood and may explain the tendency to capillary hæmorrhages by thrombosis.—F.W.M.).

Shortly after however, vomiting, faintness, and an epileptiform seizure occurred. Attacks of palpitation and headache occurred for some time after the accident and "The headaches continued at intervals for some time, and lasted certainly for some months after the accident; indeed, I cannot say they have disappeared altogether." All of the five men seemed to have suffered with these symptoms more or less. Consciousness in some of them seems to have been lost while under the influence of the poison, although there were more or less disturbances of consciousness like those of delirium. Mr. Heneage Williams for instance states: "I could still hear and understand all that was said to me as well as speak intelligibly myself, but had entirely lost physical power, besides being unable to see or recognise faces even when quite close to me, and in a tolerably good light." "I may add in reference to my mental condition during the time that I was under the influence of the gas, that, while my head was tolerably clear, there was undoubtedly a certain incompleteness in the action of my memory. The persistence of one or two ideas seems to have been very marked. An interesting fact in his narrative is that although a friend of his who was present two hours after he was brought up and just before his condition was relieved by sickness, said, 'that he spoke to me more than once without receiving any sign of recognition on my part.'" But Mr. Williams states that he distinctly remembers "a *consciousness* of the sensation of complete collapse."

THE CASES OF CARBON MONOXIDE AND NICKEL CARBONYL POISONING HERE RECORDED.

The evidence of the cerebral thrombosis and hæmorrhage was afforded in the case of poisoning by illuminating gas during life by the rigidity of the limbs, the presence

of a *plantar extensor* reflex, and the high temperature, within twenty hours of her commencing to inhale the poison. The clinical notes were not furnished in Case I. from the nickel works. In Case II. at first there was no loss of consciousness, the coma which ensued towards the end was probably the result of the toxæmia, of the pneumonia, and the extensive recent hæmorrhages. The ankle clonus and exaggerated plantar reflexes obtained in the last two days must have been the result of the hæmorrhages cutting through the projection efferent fibres of the brain and accord with the condition found in the carbon monoxide poisoning.

If we ask ourselves, what would have been the condition of these patients had they not developed a fatal pneumonia, but had recovered with multiple patches of red softening in the white matter of the cerebral and cerebellar peduncles, and to a much less extent in the centrum ovale? We reply that the softening would give place to sclerotic islets, and where these islets had coalesced, islands of sclerosis. Besides this, random tracts of fibres in the white matter of the brain, and the continuity of such descending system tracts in the spinal cord would have degenerated and been replaced by neuroglia tissue. The condition would be one of *insular or disseminated sclerosis*. If the association systems were much affected there would be some mental enfeeblement. The principal symptoms would be non-progressive intention tremors, coarse voluntary paresis, and spasticity of limbs, exaggerated superficial and deep reflexes, scanning speech and nystagmus from damage to the various systems of fibres. As the cortex cerebri was not markedly affected by the hæmorrhages, we should not expect marked disturbances of consciousness.

In fact, E. Becker (*Deutsche Med. Wochenschrift*, Nos. 26 and 27), relates the symptoms of a case of carbon monoxide poisoning in a man of 47, who after the acute symptoms had passed off developed scanning speech, intention tremor, and all the signs of disseminated sclerosis, except nystagmus, which was absent (probably the middle peduncle of the cerebellum was not damaged sufficiently).

He came to the conclusion that *multiple small hæmorrhages* had caused sclerotic areas in the brain and spinal cord.

Dr. Oliver, in his second Harben Lecture, calls attention to the fact that "the poisoning by this gas occurs in men employed at iron smelting furnaces, in the manufacture of coal gas and of soda by the Leblanc process, in the distillation of coal tar, during the explosions in coal mines, in cement and brick works, and during the incomplete combustion of fuel in domestic houses."

Moreover, he refers to a discussion on the subject of asphyxiation of blast furnace workmen at a meeting of the Iron and Steel Institute. He points out that it is the presence of carbon monoxide in blast furnace gas which is dangerous, and that the crude gas as it leaves the furnace has a perceptible odour and is visible; it can penetrate brick walls, travel by the subsoil and enter houses yards away from the furnace, causing poisoning of the inmates. If the ground is dry it can travel even considerable distances and not be perceived by those who are unfortunate enough to breathe it, for it has during its passage been filtered of the impurities which rendered it perceptible to the senses.

The escape of gas during blast furnace charging occasionally causes "gassing" of the workmen, and he narrates the history of two workmen thus affected, and states the mental symptoms manifested resembled those of general paralysis, but Dr. Oliver states that "*Questions asked of him are properly answered,*" and this hardly accords with the condition usually met with in general paralysis. The nystagmus, the slow syllabic speech and the paresis, with the exaggerated knee-jerks recorded, are more in accord with multiple foci of softening due to hæmorrhages.

Foremen of blast furnaces are familiar with "gassing" of the men; some of the men become unconscious for a brief period after charging a furnace, but in a few days they are usually well again. "In the two patients whose illness I have reported the nervous symptoms resembling those of general paralysis still persist, although it is now more than twelve months since the men became ill" (Oliver). But

general paralysis is a progressive degeneration, and the fact that Dr. Oliver does not mention new symptoms is against his view. He discusses the possibility of arsenic or lead having been present to account for these symptoms. I am of opinion that they can all be explained by the thrombotic occlusion and hæmorrhages which occur as the result of carbon monoxide poisoning, the mechanism of which has previously been discussed in full.

It is said that patients suffering from the chronic effects of carbon monoxide poisoning seldom live longer than two years (Oliver.)

The symptoms described by Dr. Alex. Scott in the *Lancet*, January 25, 1896, show that carbon monoxide poisoning may produce the most pronounced excitation phenomena, motor and mental, resulting in permanent mental impairment.

"A CLINICAL LECTURE ON DEMENTIA RESULTING FROM POISONING
BY CARBON MONOXIDE,"¹ BY ALEX. SCOTT, M.D.

This is the case of a man, aged 41, a worker at the blast-furnaces of the Clyde Ironworks, near Glasgow, at which there is a plant for the recovery of ammonia bye-products, was found lying in front of one of the flues (of the apparatus) "apparently dead." He had been exposed, it was believed, for about ten minutes to noxious fumes therefrom. After resuscitative measures, he had sufficiently recovered at the end of an hour "to bestir himself and to talk incoherently. His pulse reached 58 per minute, and the respiration became deeper." Soon after he was attacked with violent clonic convulsions which lasted for about two hours. "The mouth was open and drawn to the left side, and the muscles of that side generally were most affected. The only premonitory sign of the onset of these convulsions was a slowing of the pulse down to about 50." Four hours after he was found his condition appeared more hopeful. But soon afterwards he was suddenly "affected with tetanic contractions of the muscles, which were so violent that Dr. Lang (Scott's assistant) had to get the assistance of several men to prevent him from doing bodily injury to himself." Four hours later still, it was found that "with very short intervals the extensor muscles of the trunk and the flexors of the limbs—chiefly the arms—were contracted and rigid." Chloroform quietened the spasms. He

¹ *Lancet*, January 25, 1896.

was again treated in the open air and by oxygen inhalations, but not with any appreciable amount of success. For the following forty-eight hours the spasms increased in severity, but the intervals between had become longer in which he was "in a state of coma." These tetanic contractions gradually became less violent until, on the fourteenth day after the accident, only faint tremors of the flexor muscles were perceptible. "Only on rare occasions would the patient allow himself to be fed." "In this semi-comatose condition the patient remained for ten days." "On the fifteenth day after the accident, without any warning, he was attacked with acute mania, and had again to be put under restraint. . . . So violent was he after admission (to the infirmary) that the services of male attendants had to be procured for twenty-four hours, when he once more relapsed into his former comatose state. For the next eight days he remained *in statu quo*."

By April 13 (accident happened on March 20) he still talked incoherently, but articulation is more distinct. By May 22 the lucid intervals occur more frequently and last longer. Up till June 5 he was fed by the nurse, but now is able to sit at table and attend to his own wants.

Scott instances another case occurring in Lanarkshire Iron-works under nearly precisely similar circumstances, the patient being a young man of 20, who was maniacal for three days and quite insensible for eight days after. After the lapse of two years his health has now become "fairly good, but he still remains facile, with a weakly smile, and cannot be trusted with any responsible work."

He mentions another case published by Dr. Siegfried Stockes, of Lucerne, in *Correspondenzblatt für Schweizer Aertze*, No. 8, 1888, p. 258.

Le Dosseur has collected cases in which the following psychological troubles have followed intoxication by carbon monoxide:—(1) Aphasia; (2) acute delirium; (3) transitory chronic delirium; (4) mental confusion; (5) melancholia; (6) amnesia; (7) dementia. The intellectual troubles have not a unique pathogeny. More often, and this is especially true for the dementia, they are due to material alterations in the brain. Capillary hæmorrhage, foci of softening, arterial lesions, which can no longer be regarded as due to coincidence, but as one of the possible consequences of the intoxication. Poelchen relates six observations of softening following carbon monoxide poisoning. Both Sachs and Le Dosseur cite a number of cases.

Le Dosseur sums up his conclusions, that neither the hæmorrhages, the softening, nor the anoxhæmia are sufficient to explain all the facts, and he asserts that experiments would tend to prove that the carbon monoxide was dissolved in the serum and had a direct specific localised effect on the nerve-cell.

I should, however, remark that in considering the effect of carbon monoxide poisoning being followed occasionally by mania, melancholia, confusion, and other mental symptoms, it must be remembered that many of the cases were suicidal, and, therefore, if not actually insane at the time, probably possessed an insane and neuropathic temperament. Again, we have seen how often it is that pneumonia occurs, and the added factor of the toxæmia does not warrant the assertion that carbon monoxide poisoning *per se* produces the symptoms of delirium. In fact, the experiences of Le Neve Foster negative this conclusion.

VI.—THE POSSIBILITY THAT SOME LITTLE UNDERSTOOD OR UNDIAGNOSED MORBID CONDITIONS WHICH TERMINATE FATALLY IN SOME INSTANCES, MAY BE THE RESULT OF CARBON MONOXIDE POISONING

Dr. Tatham, Statistical Superintendent to the Registrar General, stated in his evidence before the Commission that it might be assumed that there were more deaths from this cause than were registered. The males outnumbered the females by five to one, which points, as one member of the Commission indicated, to industrial causes being the most important factor.

Dr. Haldane, in the Appendix, calls attention to an investigation of Pettenkofer who showed that the poisoning may occur in houses where no gas is laid on, and in the cases given, the cause of illness or death was not at all suspected at first, the gas having lost its characteristic smell during its passage through the earth, and only getting into the houses at night or during the cold weather. In the first case recorded by Pettenkofer the illness was diagnosed and treated as typhoid fever, and a

nurse and another patient were believed to have been infected by the patient. A slight smell noticed was attributed to drainage and to flowers in the room. The patient most seriously affected was, when pronounced by the doctor to be moribund, saved by a friend who insisted on his removal to another house, as she detected the smell of gas.

Other similar cases are recorded by Beifal and Polack (*Zeitschrift für Biologie*, xvi., p. 314), in one of which death had already been certified by the doctor in attendance (the illness had lasted two days) as due to another cause, when the occurrence of further cases of severe illness among relatives who had come to the funeral led to an examination of carbon monoxide in the blood of the patients, and a *post-mortem* examination of the body. Cases of *illness* and death attributed to "sewer gas," "blood-poisoning," "cardiac failure," &c., are, in all probability, sometimes caused by leaky gas mains. In some cases the gas may get into the houses through the drains, and render sewer air, which is ordinarily quite harmless, not only poisonous but also explosive from the quantity of gas mixed with it. The danger is increased by gas percolating through the soil as it becomes deodorised.

The Departmental Committee finally, in their report, state: "Bearing carefully in mind that it is not desirable to place special restrictions upon the development or management of the trade unless, without such restrictions some serious effect upon public safety or convenience is to be feared, we nevertheless consider that the unrestricted distribution and use of carburetted water gas would constitute a substantial danger, and we submit that it ought to be prevented. It is to be observed that the danger is not confined to accidents. The American figures, at least, show an increasing use of gas for suicidal and even homicidal purposes. The facility with which murder (particularly child murder), having all the appearance of accident, could be committed by simply turning on, in a small room, a jet of gas containing a large proportion of carbon monoxide seems to us an additional reason for restricting the use of carburetted water gas."

In the early part of the year 1901 there were two deaths at No. 28, Cullum Buildings, and at the inquest it was clearly proved that the deaths were due to gas poisoning: a sample of the gas collected a few days before the inquest was found to contain 30 per cent. of water gas.

The London County Council, recognising the importance of the matter of water gas in the London Gas Supply, instructed their chemist, Dr. Clowes, to make a systematic investigation of the London Gas Supply as to the presence of water gas. This was done between June 1 and May 27, 1902.

Recommendation.

The information obtained from an examination extending over a year proves that the Gas Companies are able to supply gas of the statutory illuminating power, even when the quantity of carbon monoxide in their gas does not exceed 12 per cent. I recommend, therefore, that if any of the Gas Companies which are supplying gas to London are using water gas, when the Board of Trade introduce a measure limiting the extent of enrichment of coal gas by means of carburetted water gas, this committee should seek to have inserted in the bill a clause stating that the whole amount of carbonic oxide present in the gas, as it is supplied to London, shall not exceed, at any time during the twenty-four hours, 14 per cent. by volume.

FRANK CLOWES.

Chief Chemist.

June 12, 1902.

WORKS OF REFERENCE.

- [1] Report of the Departmental Committee appointed to enquire into the Manufacture and Use of Water Gas and other Gases containing a large proportion of CO. 1899.
- [2] The Investigation of Mine Air, by Sir C. Neve Foster and J. S. Haldane, F.R.S.
- [3] The Harben Lectures, 1895. Dr. F. T. Oliver.
- [4] * Die Kohlenoxyd-Vergiftung in Ihrer Klinischen, Hygienischen und Gerichtsärztlichen Bedeutung von Dr. Med. Willy Sachs. Braunschweig, 1900.
- [5] * Des Troubles Intellectuels consécutifs à l'Intoxication oxycarbonique. Thèse de Paris, par Louis Le Dosseur.
- [6] Nickel Carbonyl. Proceedings Phil. Soc., Glasgow, vol. xxii. McKendrick and Snodgrass.
- [7] Text-Book of Medical Jurisprudence, Toxicology and Public Health. Glaister.

* A very complete Bibliography is given in these two works, which it is not necessary to repeat here.

VII.—EXAMINATION OF THE CENTRAL NERVOUS SYSTEM
IN A CASE OF POISONING BY ILLUMINATING GAS.

BY F. W. MOTT, M.D., F.R.S.

Suicide of a mother and murder of two children by illuminating gas. Coma, at first accompanied by signs of irritative lesions of the central nervous system, later followed by signs of paralytic lesions. Pneumonia and death four days after inhalation. Post-mortem: Naked eye hæmorrhages throughout the white matter of the brain. Microscopic hæmorrhages in the medulla and other parts. Basophil reaction of the red corpuscles in sections of the vessels. Fatty degeneration of the heart, cerebral capillaries, and of the epithelial cells of the liver and kidneys.

The following notes have been kindly supplied by my late house physician, Mr. H. Bourdas.

The patient, Mrs. —, was admitted under the care of Dr. Mott, at Charing Cross Hospital, January 12, 1906. On January 11, 1906, she came to London with her two children and went to an hotel. The same evening she had dinner and afterwards took the children to the theatre. Returning home about 11.30 p.m., she retired to her room with the two children. Next morning about 9 a.m. she was called but no answer was obtained, so she was left alone. Later on in the morning she was called again, and on receiving no answer the attendant informed the manager of the hotel and the door was broken down. The room was found full of gas, all openings into the room were found stopped up, the burner taken off the gas bracket and the gas full on. The two children lying on the bed were dead, and Mrs. — in an unconscious state. A doctor was immediately sent for and the patient removed to another room where artificial respiration, stimulants, &c., were resorted to. As she did not recover she was brought to the hospital in the afternoon of January 12.

On admission, the patient was in a comatose condition breathing stertorously. There was a reddish pink colour about the face and lips, and the limbs were motionless. The cheeks puffed in and out during respiration; the pupils were very small, almost pin-point, and there was sluggish re-action to light. The corneal reflex was obtained. Chiefly on the condition of the pupils being so small, it was thought that possibly she had taken opium in some form, so the stomach tube was passed and the stomach washed out with potassium permanganate, solution gr. x., oi. iii. A hypodermic injection of atropine was also administered. This was done

in the casualty room. Oxygen gas was then freely given the respiration stopping at frequent intervals, artificial respiration was resorted to. She was then taken up to the ward and put to bed. Her temperature at this time was found to be 99.4, respirations 18, pulse 116, regular, good volume; but at 10 p.m. the temperature had gone up to 105°, with respirations 54 and pulse 134. The patient then burst into a profound perspiration and the arms and legs became quite rigid. The knee-jerks were diminished, and the plantar extensor reflex was obtainable. The pupils were somewhat larger (hypodermic injection of atropine sulph.), and reacted to light and the corneal reflex was easily obtainable. The breathing became less stertorous, but very irregular and frequently arrested. Oxygen was now given continuously. At 12 p.m., the patient's temperature had come down to 103.4°, but her respirations had risen to 60 and pulse to 156, and the patient was now perspiring freely. A catheter was passed and 28 ozs. of urine withdrawn.

January 13. Patient was still comatose and her breathing very irregular with frequent long pauses, when patient became very cyanosed and artificial respiration had to be performed and oxygen freely given, resulting in improvement which took place almost immediately. Her breathing was of the Cheyne Stokes character. Temperature 101°, pulse 116, respirations 48. The arms and legs were rigid, more especially on the left side. The knee-jerks could not be obtained, but there was a well-marked plantar extensor reflex. The pupils were of medium size and reacted sluggishly to light. The corneal reflexes were obtained. 12.30 p.m. A nutrient enema of peptonised milk, 5 ozs. was given and retained. Oxygen still given. Extremities cyanosed. Face less flushed. At 1.15 p.m. breathing stopped for three minutes but continued again for about three quarters of an hour fairly regularly, followed by another pause of three minutes, after which it was quicker for thirty-two minutes then another pause of one minute. There were some spontaneous movements of the arms in the morning, but during the evening the rigidity of both arms and legs was less marked and the extremities were not cyanosed. At 4.30 p.m. a nutrient enema of 5 oz. peptonised milk was again given and retained. The pauses of breathing were frequent occurring every ten minutes. The patient had incontinence of urine at intervals during the day. 10 p.m. Temperature 103°, pulse 140, respirations 48. The patient was still in a comatose condition, breathing very irregularly. Oxygen was given continuously and with artificial respiration at intervals. The hands and arms were very rigid, more marked on the left side, the face very flushed and the lips blue. Occasionally there were spontaneous movements of the upper extremities. 12.35 a.m.,

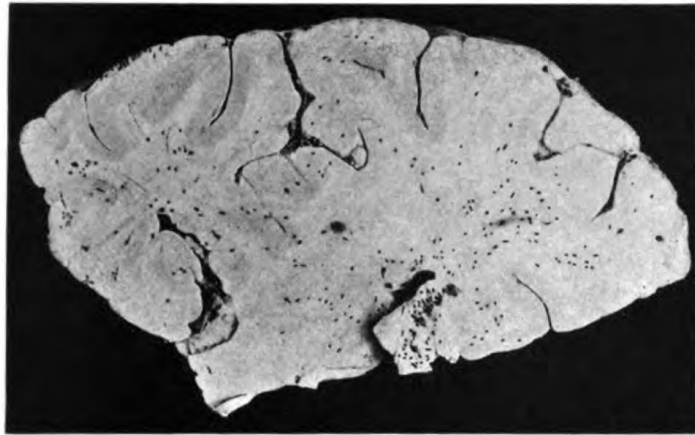


FIG. 3.—OBSERVE THE HÆMORRHAGES IN THE WHITE MATTER, AND ESPECIALLY THE CORPUS CALLOSUM. $\frac{1}{2}$ Natural Size.



FIG. 4.—OBSERVE THE PUNCTIFORM HÆMORRHAGES IN THE CORPUS CALLOSUM. $\frac{1}{2}$ Natural Size.

there was a pause in the breathing for five minutes, after which it became quieter. Patient had nutrients of peptonised milk, 5 ozs., with $\frac{1}{2}$ oz. brandy in every alternate one.

Dr. Mott saw the patient and said that grave changes had occurred in the central nervous system, probably hæmorrhages in the white matter of the brain and medulla and that death would certainly occur. He made an examination of the blood and noted that some resistance was offered to pricking of the finger. A drop of blood diluted gave a pinkish colour and examined spectroscopically two bands were seen which persisted even after addition of ammonium sulphide although a band of reduced hæmoglobin filled up the intervening space.

January 14.—10 a.m., temperature 103° , pulse 120, respiration, 56. Breathing was regular and rapid, and the face flushed. The rigidity of the arms and legs had passed off. The patient perspired freely all the day but still remained comatose. All four limbs were flaccid. Pupils medium size, reacted sluggishly to light, and the corneal reflex was present. Knee jerk was not obtainable, nor was the plantar extensor reflex. Patient developed herpes on the lips at 6 p.m., and her temperature went up to 105.2 , pulse 150, respiration 56. She was fed nasally. A cough developed and tubular breathing could be heard over right upper lobe.

January 15.—Patient was still quite comatose. Highest temperature 105° , pulse 156, respirations 60 regular. Right upper lobe of lung in a pneumonic condition. The patient had not moved any of her limbs since they became flaccid. Eyes remained the same. Knee jerks were absent and Babinski's sign had disappeared. The pulse was very rapid, weak and markedly dicrotic. The patient still perspired freely. At 10 p.m. her temperature went up to 106.2 , pulse 14, and respirations 56. She was tepid sponged after which the temperature came down to 104° , but at 12 a.m. it rose again to 107° , when she was again sponged. At 2 a.m. January 16, respiration became much less frequent, the pulse scarcely perceptible, and at 2.30 a.m. she died, never having regained consciousness. The time elapsing between inhalation of the gas and death was therefore exactly four days. January 16, a *post-mortem* examination was made.

Body of a well nourished woman. Rigor mortis well marked. Slight *post-mortem* staining in dependent parts. The skin presented an appearance like old wax.

Thorax: about $\frac{1}{2}$ oz. blood stained serum in pericardium. Right pleura obliterated by old adhesions; left pleura, healthy; oesophagus, healthy; larynx, healthy. Large bronchi injected and contain a little blood-stained mucoid material.

Lungs.—Left: Base shows marked hypostatic congestion.

Right: Shows patch of early pneumonia at posterior aspect of base of upper lobe about the size of an orange. Adjacent portion of apex of lower lobe shows consolidation, due to early pneumonia.

Heart.—Weight 10 oz., flabby. Muscle of both ventricles shows extensive fatty degeneration. Valves, healthy. Mediastinal glands apparently healthy.

Abdomen.—Liver, 3 lb. 2 oz. in weight. Gall bladder distended with green bile. Liver substance markedly fatty. Kidneys, $4\frac{1}{2}$ oz. and 5 oz. respectively. Cortex markedly injected. Substance appears flabby and cloudy. Adrenals, healthy. Spleen, healthy. Pancreas, healthy. Bladder, healthy.

Uterus.—Subinvolved. Appendages healthy. R. ovary contains large Graafian follicle.

Brain.—Weight 2 lb. 11 oz. Convolutional pattern complex. Pia arachnoid not thickened. There are various congestive patches about external and mesial surface of hemisphere; all indications of subpial hæmorrhages. Weight of each hemisphere, 1lb. 2oz. Weight of pons and cerebellum, 6 oz.

On slicing pons in lower part congested vessels are seen suggesting thrombosis or minute hæmorrhages. No visible hæmorrhages in medulla.

The right hemisphere was cut up and throughout the white matter, especially in the internal and external capsules and corpus callosum are aggregations of hæmorrhagic points of varying size, suggesting either thrombosis of perforating arteries or hæmorrhages into their sheaths—probably both.

Throughout the white matter of the centrum ovale are punctiform hæmorrhages quite similar to those seen in No. 2 Case of Nickel Carbonyl poisoning. These hæmorrhages became especially distinct after hardening the left hemisphere in 5 per cent. formalin solution and then slicing it in vertical sections. (*Vide* photographs—half natural size, figs. 3 and 4.)

HISTOLOGICAL EXAMINATION OF THE TISSUES.

Liver, heart and kidneys were placed in Marchi fluid and after hardening, sections were cut to ascertain if there was fatty degeneration.

The *heart muscle* showed very marked fatty degeneration, every fibre showed a cloud of small black particles indicating degeneration in the early stages.

The *liver* also showed fatty degeneration, every cell containing black stained particles.

The *kidney*. The most fatty degeneration was observed



FIG. 5.—SMALL VESSEL RUPTURED WITH HÆMORRHAGIC EXTRAVASATION INTO THE TISSUES. Magnification 90×1 .



FIG. 6.—PHOTOMICROGRAPH SHOWING FATTY DEGENERATION OF THE WALLS OF SMALL VESSELS. The black staining by Marchi method indicates the change. Magnification 100.

in the epithelium of the convoluted tubules. It is, however, not nearly so marked in this organ as in the liver.

The *lung* shows first stage of pneumonic consolidation. The alveoli are filled with exudation and blood.

The cortex cerebri.—The vessels of the cortex are dilated, but it is in the sub-cortical white matter especially, that one finds the greatest amount of congestion and hæmorrhage, and the rupture of small vessels. The rupture is sometimes into the substance of the brain, sometimes into the perivascular sheath. Many of the small vessels show indications of glia cell proliferation in their neighbourhood and leucocytic infiltration of the sheath. The endothelial cells of the capillaries appear swollen and some of the nuclei are undergoing division. Stained by Marchi fluid these give a black stain indicating degenerative changes of the walls (*vide* photomicrograph, figs. 5 and 6.) The most marked vascular degeneration and hæmorrhages are seen in the white matter of the centrum ovale, especially in the white matter of the occipital lobe.

The medulla.—The vessels are intensely congested and in the sections stained with polychrome and eosin the red corpuscles are seen to take the blue stain instead of the red. There are very few hæmorrhages and those that are found, are into the sheath of the vessel, not into the substance of the brain. The ganglion cells show little alteration in form, but there is a general diffuseness of stain. This may have been due to the high fever.

MICROSCOPICAL EXAMINATION OF A BRAIN FROM CASE I. FROM THE NICKEL CARBONYL WORKS.

The brain which had been cut in slices was forwarded to me in a large jar containing spirit, having been thus hardened in this fluid the methods of examination were limited to the Nissl process of staining for showing changes in structure. Portions of various parts of the hemispheres including the motor area, the internal capsule, centrum ovale, basal ganglia together with portions of the pons and medulla at several levels, were taken for examination.

It was noticed that throughout the hemispheres the vessels were engorged with blood and the brain substance appeared beset with capillary hæmorrhages varying in size from the point to the head of a pin. There were no naked eye appearances of hæmorrhages in the pons and medulla. They were most noticeable in the sub-cortical white matter.

Ten portions of the brain were examined. The sections were made of the uniform thickness of $10\ \mu$ after embedding in paraffin, and the staining was by the Nissl or some modification of the Nissl method. Several hundred preparations have been made and the following facts were ascertained by examination of them.

(1) The cells of the whole of the specimens (as a rule), showed some chromolytic changes. In the cortex they were less marked than in the pons and medulla. The very large Betz cells of the cortex showed, as a rule, nearly a normal appearance. The cells of the pons and medulla were more affected than those of the cortex, and hardly a healthy cell could be seen in the following nuclei: the vagus, nucleus teres, the spinal accessory lying in the floor of the fourth ventricle; also the nucleus ambiguus showed marked changes indicating early organic change in the form of coagulation necrosis.

It is possible, therefore, to associate these changes with the symptoms of cardiac and respiratory failure observed during life. At the same time it must be remembered that the autopsy was made forty-eight hours after death, and that, therefore, while I believe this change was probably in part *ante-mortem*, I could not with certainty state that it *may not* have been in part or wholly due to *post-mortem* change.

The condition, however, of the small vessels and the blood contained in them (especially noticeable in the pons and medulla), suggests the probability that the poison had affected the nuclei mentioned especially. The small vessels in their immediate neighbourhood showed endothelial proliferation and contained a relatively enormous number of leucocytes, polymorpho-nuclear being by far the most abundant, evidence of acute inflammatory action. It may

be remarked, as a rule, the vessels in the medulla showed only disintegrated red corpuscles. Photomicrographs illustrative of these various facts have been made and were forwarded with the report.

Whilst I could find no hæmorrhages into the substance of the pons and medulla, careful search of a number of sections revealed general venous engorgement, with occasional hæmorrhagic extravasations into the perivascular lymphatic sheath.

The hæmorrhages in the brain were more numerous than I have ever seen before; they appeared to be due to rupture of the walls of the small capillaries, and were apparently mostly of recent origin. In some instances the corpuscles of exuded blood appeared to be morphologically perfect, in others they had run together into a red amorphous mass, while sometimes the corpuscles of the extravasated blood were covered with very minute brownish orange crystalline bodies, many of which appeared tetrahedral in shape.

Conclusions.

I have examined a large number of brains from persons affected with many forms of disease, including blood diseases; *e.g.*, pernicious anæmia and lukæmia, asphyxial states from lung disease, status epilepticus and tracheal obstruction, but I have never seen such extensive and universal capillary hæmorrhage in the brain as in this case. I conclude, therefore, that there was probably an acute fatty change of the capillary walls produced by the poison. The swelling and proliferation of the endothelial cells of the capillaries would support this view, although owing to the method of hardening I was unable to apply the osmic acid reaction. The immense number of polymorpho-nuclear leucocytes in the vessels and the changes in the blood described all point to an acute blood change with inflammatory reaction. The morphological changes observed in the ganglion cells so especially observable in certain of the nuclei of the floor of the fourth ventricle may have been due to *post-mortem* change, but it must be remembered



FIG. 7.—PHOTOGRAPH OF THE MESIAL SURFACE OF THE RIGHT HEMI-
SPHERE OF THE BRAIN OF CASE 2. From Nickel Carbonyl Works, showing
the hæmorrhage in the cut surface of the divided corpus callosum.

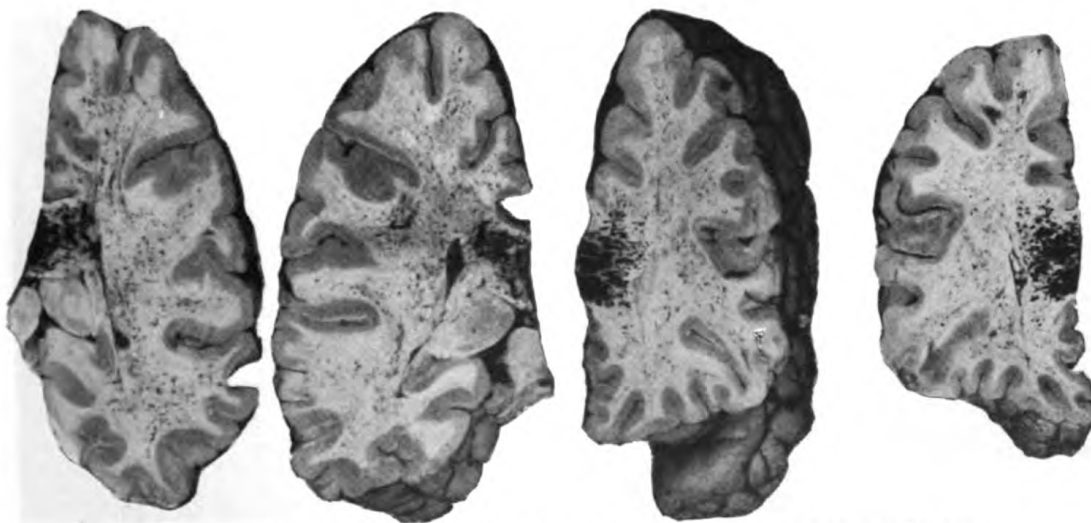


FIG. 8.—PHOTOGRAPH OF SECTIONS OF THE BRAIN FROM CASE 2, Nickel
Carbonyl Works, showing hæmorrhages in the white matter, especially of
the corpus callosum and internal capsule.

that although nearly forty-eight hours elapsed between death and the removal of the brain, that the weather was cold and carbon monoxide poisoning tends to preserve the tissues from putrefaction. These facts taken in conjunction with the obvious changes in the blood and blood vessels, together with the extraordinary number of capillary hæmorrhages of the brain, all of which must have occurred *ante-mortem*, make it probable that the changes observed in the cells of the cardio-respiratory nuclei were *ante-mortem* and associated with a marked dyspnœa observed during life.

Chemical Examination of the Brain for Nickel.

About 400 grammes of the brain were taken and incinerated, then transferred to a platinum crucible and fused for some time with fusion mixture, with the occasional addition of a little potassium nitrate.

This converted all the phosphates present into a soluble condition leaving the metals as insoluble carbonates. The phosphates were removed by well washing with hot water. The iron was separated by repeated precipitations with ammonia and ammonium chloride, mother liquors evaporated to small bulk and made acid with acetic acid. Sulphuretted hydrogen was then passed into the solution (hot) for fifteen minutes. No trace of nickel sulphide was discernible.

REPORT ON THE BRAIN OF CASE II. FROM THE NICKEL CARBONYL WORKS.

Brain received in 5 per cent. formalin, May 29, 1903.

The pia-arachnoid, especially of the spinal cord and the base of the brain, have a rusty appearance.

The hemispheres are soft; whether this is due to the distension of the ventricles or softening of internal substance, I am unable to say. The cortical substance appears firm. The pons was cut through and separated. The two hemispheres were then divided in the middle line; a condition was found in the corpus callosum which I have never seen before. The whole of the cut surface presented the

appearance of punctiform hæmorrhages, and the two extremities show very little white matter on account of these hæmorrhages. On slicing up the hemisphere the whole of the white matter was seen to be the seat of similar hæmorrhagic extravasation. On examining with a lens it was observed that the blood was bright red in colour and apparently had escaped from the vessels into the perivascular sheath and tissue around. The grey matter shows comparatively little change, but with a lens hæmorrhages can be found. (*Vide* photographs, figs. 7, 8 and 9.)

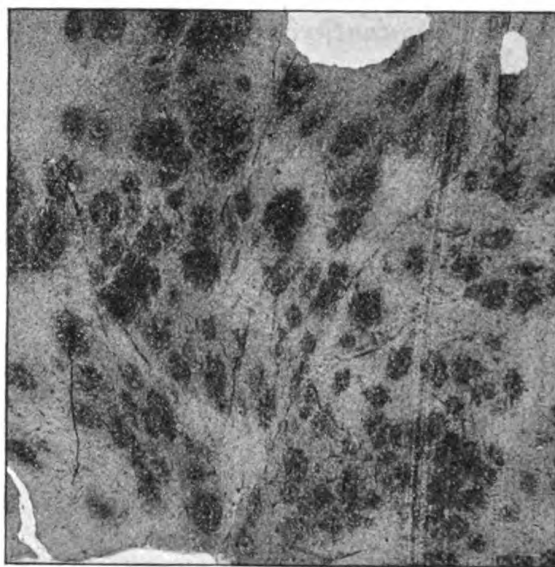


FIG. 9.—SECTION OF CORPUS COLLOSUM, stained with methyl blue and eosin, showing hæmorrhages. Magnification, 10×1 .

Cerebellum.—The peduncles of the cerebellum especially and the white matter of the lateral lobes to a less extent, show congestion of vessels and hæmorrhages.

Pons and Medulla show likewise the same vascular changes but to a less degree. They are most marked however in the pyramids but there are naked eye hæmorrhages in the floor of the fourth ventricle in a few places.

Spinal Cord.—There are hæmorrhages in both grey and white matter in the whole of the cervical and upper two

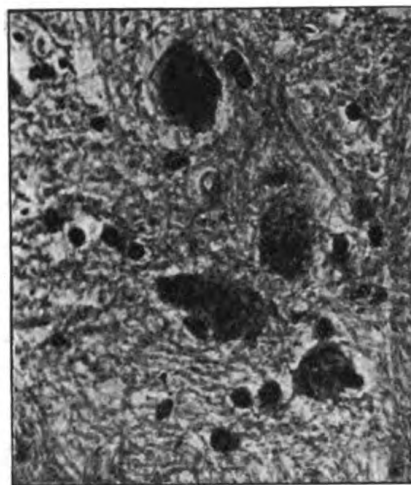


FIG. 10.—MEDULLA OBLONGATA (Case 2), showing cells in Bechterew's nucleus. The cells are diffusely stained throughout, and there is a proliferation of young neuroglia cells in the neighbourhood. Magnification, 350×1 .

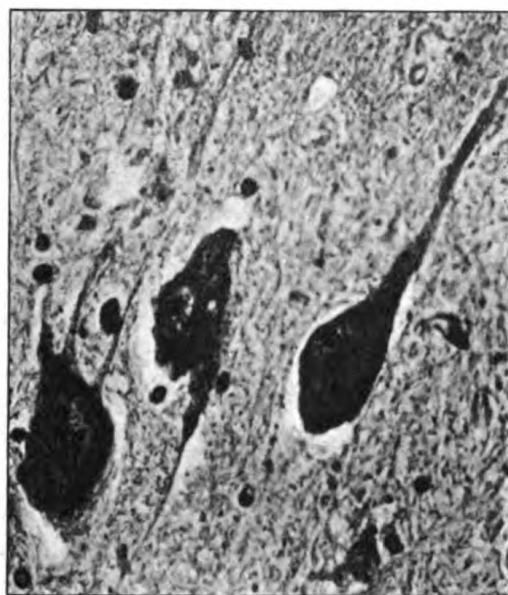


FIG. 11.—SECTION OF MEDULLA OBLONGATA (Case 2), showing three large motor cells in nucleus ambiguus. There is a diffuse chromolytic staining of the cells and processes quite different to the hypoglossal nucleus where the Nissl granules are fairly normal in appearance. Magnification, 360×1 .

or three dorsal segments; only this upper portion of the spinal cord was sent. In some places the anterior horns appear to be damaged, especially about the third and fourth cervical segments.

The membranes are nowhere thickened and the general appearance indicates an acute toxic process; very striking is the red character of the blood in the hæmorrhages.

Microscopical Examination of the Brain and Spinal Cord.

Two methods were employed. Duplicated portions of the brain and spinal cord were taken from various regions. *e.g.*, cortex, corpus callosum, corona radiata, cerebellum, pons, medulla (four blocks at different levels) and spinal cord (four blocks at different levels).

One set was placed in alcohol, changed several times, and eventually embedded in paraffin, cut in series and stained by the Nissl and various modifications of the Nissl method. The duplicate set were placed in Müller's fluid and changed several times to wash out the formalin. After a fortnight placed in Marchi fluid; in order to hasten the process of penetration, the Marchi reaction was conducted in a warm chamber at a temperature of 37° C. for a week.

Eventually sections were cut in celloidin. It may be stated that the changes by the Nissl method correspond in great measure to those described in the previous case examined. The observations are, however, of far greater value as in this case the tissues were removed eight hours after death, and therefore the fallacy of *post-mortem* change is avoided.

Again the Marchi method for degeneration could not be applied in Case I. because the brain had been placed in spirit.

Microscopical Examination of the Grey Matter of the Central Nervous System by the Nissl Method.

Most of the cells of the cerebral cortex which possess Nissl granules, show diffuse staining and absence, or partial absence, of the granules in the cell body and processes.

The cells of the pons and cerebellum present similar changes.

The Medulla.—The cells of the various cranial nuclei of this portion of the central nervous system were carefully examined in a large number of sections, and some interesting facts were revealed; for whereas the cells both small and large of the hypoglossal and facial nuclei showed little or no change, the cells of the respiratory nucleus (of Bechterew) situated in front of the hypoglossal along the median raphe, and of a similar type were in all sections changed; the protoplasm of the cells and their processes showed no granules, and were diffusely stained. The same applies but to a less degree to the cells of the nucleus ambiguus and nucleus lateralis (*vide* photomicrographs, figs. 10 and 11).

It is impossible to make any reliable statement with regard to the sensory cells of the medulla.

Spinal Cord.—Different segments in the cervical and dorsal regions were examined. Single cells or groups of anterior horn cells were seen fairly normal in appearance by the side of other single cells or groups of cells profoundly changed.

These facts suggest that the changes observed cannot be due to a general increase in temperature of the body, for in such cases the cells are universally affected. Probably a combination of factors have conspired together to produce the cell changes. They may be thus enumerated in order of importance.

(1) Circulatory disturbances caused by the presently to be described vascular changes of thrombosis and hæmorrhage.

(2) Stress on account of their increased activities under unfavourable conditions of nutrition, notably anoxæmia.

(3) Auto-toxic conditions arising from the presently to be described degeneration of nervous tissue.

(4) Rupture of the axis cylinder processes by the hæmorrhages.

(5) Hyperpyrexia.

(6) Establishment of a vicious circle in which cardiac and respiratory failure play the prominent part.

Vascular changes in the grey and white matter.—Naked eye examination shows the white matter to be the seat of, by far, the greatest amount of hæmorrhages. They have occurred especially therefore in that part of the central nervous system where there are terminal arteries, *viz.*, where each arterial twig breaks up into a capillary network with a wide mesh situated around bundles of fibres. These capillaries have very thin walls and owing to certain anatomical

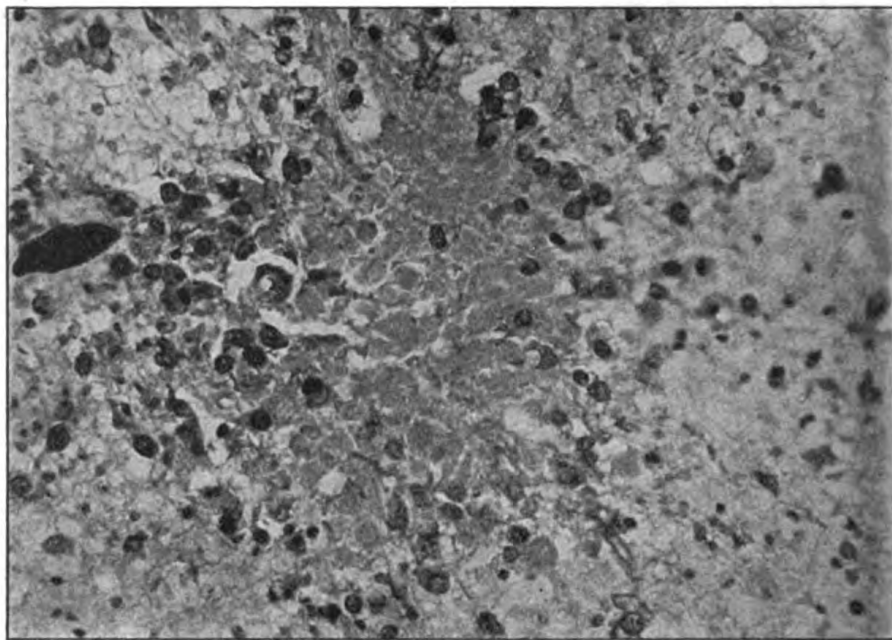


FIG. 12.—OLD HÆMORRHAGIC SOFTENING WITH SURROUNDING ZONE OF LEUCOCYTES AND PROLIFERATING NUCLEI OF GLIA CELLS. Magnification 400×1 .

conditions more easily rupture than those in the grey matter. The distribution of the capillary network around bundles of fibres, explains the microscopic appearances presented by the hæmorrhages in the white matter. The hæmorrhages are not all of the same age, some are quite recent, others are much older.

These hæmorrhagic conditions will now be described :—

(a) Central area of degenerated nerve fibres surrounded by a large number of polynuclear leucocytes, and prolifera-

ting glia nuclei, but hardly any red blood corpuscles visible now. These are old capillary hæmorrhagic foci. Stained by Marchi method, the central portion and the leucocytes around, contains a large number of black stained granules (*vide* photomicrograph, fig. 12).

(b) Foci of capillary hæmorrhages of more recent date in which there is a central area of degenerated fibres staining a dirty pink (by methylene blue and raffnain) surrounded with leucocytes, lymphocytes and red blood corpuscles (*vide* photomicrograph, fig. 13).

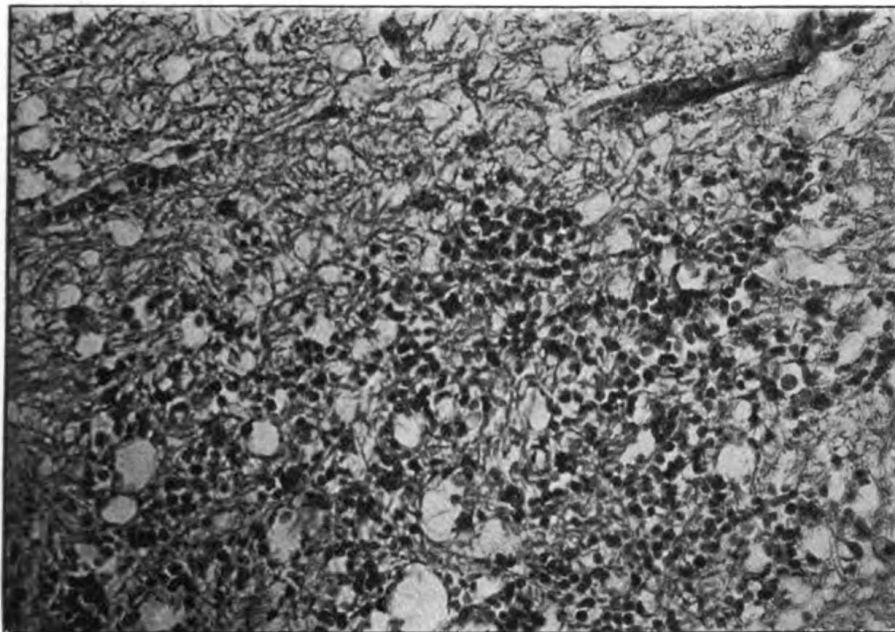


FIG. 13.—RECENT CAPILLARY HÆMORRHAGE IN WHITE MATTER OF INTERNAL CAPSULE. Magnification 280×1 .

(c) Foci of quite recent capillary hæmorrhage in which there is only extravasation of red blood corpuscles into the tissue; very few leucocytes and no glia cell proliferation. Stained by the Marchi method, only a few or even no black particles.

Signs of inflammation.—The vessels appear for the most part to be in a state of acute inflammation. The arteries and veins show both in the grey and the white matter leucocytes in great abundance in the perivascular

lymph sheaths. The capillaries exhibit almost everywhere a proliferation of nuclei (*vide* photomicrograph, fig. 14). There is a great excess of leucocytes and glia nuclei every-

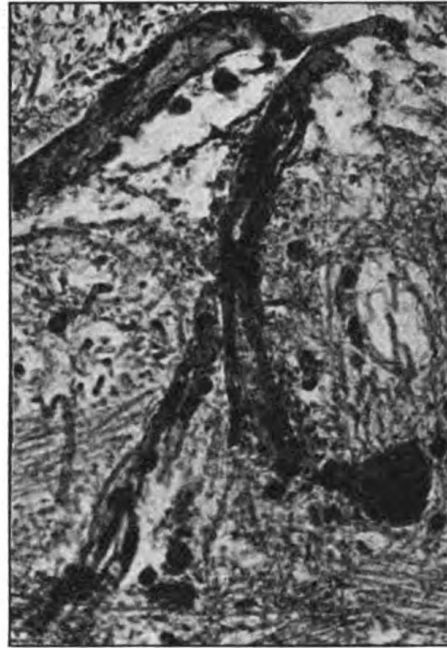


FIG. 14.—SECTION OF MEDULLA OBLONGATA, showing small vessel exhibiting nuclear proliferation of the endothelial cells. Magnification, 350×1 .



FIG. 15.—SMALL VESSEL OF MEDULLA OBLONGATA (Case 2), showing the lumen blocked by an organising thrombus consisting of white corpuscles and fibrin. Magnification, 600×1 .

where in the nervous tissues ; sometimes a crowd are seen together around a ganglion cell in the pericellular space, as if active proliferation had taken place.

In the medulla about the level of the top of the calamus an artery was cut in a series of sections which was filled with fibrin and leucocytes, evidence of vascular thrombosis (*vide* photomicrograph, fig. 15).



FIG. 16.—RECENT CAPILLARY HÆMORRHAGE INTO WHITE MATTER. Degenerated fibres stained black by Marchi method. Section of magnification.

Examination by the Marchi method.—Sections were cut in celloidin to show the fibres in longitudinal and transverse section.

The results are most striking. Every part of the nervous system examined shows degenerating and degenerated fibres in abundance. The degenerated fibres were not

most numerous where the hæmorrhages were most abundant, *viz.*, the corpus callosum ; in fact these regions showed practically hardly any, because the hæmorrhages in this region were most recent, and a sufficient time had not elapsed. It takes six days after the lesion before degeneration will manifest itself, and a few days more than this before it becomes very obvious, so that most of the degeneration which we see so manifest and extensive in the white matter of the cerebral cortex of the cerebellum, the corona

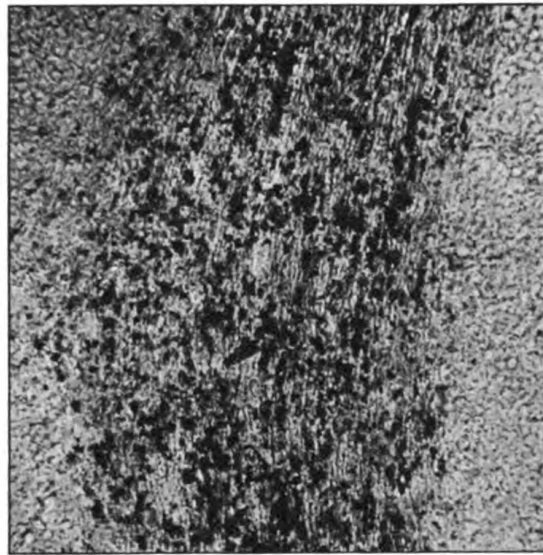


FIG. 17.—SECTION OF CEREBELLUM (Case 2), stained by Marchi method. Magnification, 180×1 .

radiata, the pyramids, the antero-lateral and posterior columns of the spinal cord probably dates from lesions caused before, at the onset, or shortly after the onset of the attack. The degenerative changes are doubtless to be associated with the older foci of hæmorrhages which have been described. The anterior and posterior roots show also degenerative changes but to a much less degree.

The fact that the degenerated fibres can be seen in their long axes disposes of any argument that this is not a

true degenerative process (*vide* photomicrographs, figs. 16 and 17).

Summary.

It is unfortunate that the heart, the vagus and phrenic nerves were not sent to me for examination; but the facts described in the examination of this brain convinces me that the profound changes which have occurred in the central nervous system may be associated (*a*) with the poison; (*b*) with the clinical symptoms presented by the patient, from the onset of the disease to his death.

The changes in the cardiac and respiratory nuclei of the medulla may be possibly associated with the rapid respiration and accelerated heart action although it is quite probable that fatty degeneration of the heart and hyposstatic pneumonia may have also contributed.

The increase of the deep reflexes was doubtless due to degeneration of the pyramidal tract systems. The onset of delirium terminating in coma may be associated with the recent extensive hæmorrhages throughout the white matter of the brain, and the marked changes in the cerebral cortex.

Unfortunately I have been unable to obtain the *post-mortem* notes of these cases though I understand both developed pneumonia before death occurred, in this respect resembling the coal gas poisoning. In Case II. it is interesting to note that the patient for several days previous to his giving up his work had manifested symptoms of the poisoning, complaining of pains at the epigastrium and migraineous symptoms. It is probable that the latter were due to the oldest foci of hæmorrhage found in the white matter of the central nervous system. The loss of consciousness preceded by delirium which occurred a few days after he took to his bed may be associated with the onset of pneumonia and further hæmorrhages and cerebral changes and the profound coma towards the termination of life with the most recent and extensive hæmorrhage.

May 31, 1903.

*Some Particulars concerning the Illness of Case II., by
John Jones, M.D.*

State of Consciousness.—Patient first seen on May 20. Took to his bed on the evening of the 21st; consciousness quite unaffected until evening of 24th, when there was slight rambling (temperature 103.8°). On the 26th patient was more or less unconscious but was easily roused, and when requested put out his tongue, winked either eye, and recognised those about him rapidly: relapsing into a semi-comatose condition. This condition lasted till within twelve hours of death, when coma became more profound, death occurring at 10.15 a.m. on May the 28th.

Pupils.—Equal, slightly dilated, reacted to light and accommodation, no strabismus, no ptosis, &c. On the 24th both pupils were contracted and remained so for about twelve hours. Patient had had two hypodermic injections of morph. sulph. $\frac{1}{4}$ gr., atropine sulph. $\frac{1}{150}$ gr. on that day. Pupils returned afterwards to former state and remained so until death.

Pulse and Heart's Action.—Heart's action kept good until evening of the 24th, when dilatation could be distinctly found on percussion, then he gradually got worse. Pulse exhibited no irregularity throughout as regards rhythm.

Date :	May 20	May 21	May 22	May 23	May 24	May 25	May 26	May 27	May 28
Pulse ..	68	80	90 94	116	120 132	132	130	132 156	168
Respiration	16	22	38 46	56	60 62	64	60	60 72	54
Temperature (average)	98°	98.4°	100.2°	100.6°	103.2°	104°	103.2°	103.8°	105.4° 107.2° rectum

Respiration, Diaphragm, &c.—Rate given above. *No orthopnea* whatever. Patient would lay quite flat on his back breathing 60 per minute, although perfectly conscious. Diaphragm in action throughout. These patients complain for the first four or five days of an acute pain in the epigastric region, which becomes worse on taking a deep breath. In some cases this pain is referred to back of sternum; again, in a few cases the pain is *post-manubrial*.

Muscles, &c.—No paralysis. Deep reflexes present to end. *Ankle clonus* got on last two days. *Superficial reflexes.*—Conjunctival reflex persisted to within one hour of death. *Plantar reflexes* present to within eight hours of death, and were *greatly exaggerated*. The patient was taking strychnine in moderate doses during the first week of his illness. He could not be made to

swallow his milk, &c., on the 26th and 27th. He would retain it in his mouth for several minutes, and then suddenly squirt it out beyond the foot of the bed. By giving him a little oxygen previously he could be made to swallow better. It was suggested by some of the medical men in attendance that there might be *slight trismus* present.

Sensation. Special Senses.—No loss of sensation, &c. Special senses unaffected until morning of the 27th, when, owing to mental state it was difficult to decide exact condition of special senses for last twenty-four hours of life.

Time elapsed between onset of Symptoms and Death.—Patient worked eleven hours on May 20. He died on the morning of May 28. Had had pain in his stomach and migraine for a day or two previous to giving up work. Time and date of exposure to poison difficult to ascertain correctly. Time elapsed between death and placing brain in formalin solution eight hours.

ACUTE ADDISON'S DISEASE WITHOUT PIGMENTATION, PAROXYSMIS OF VOMITING BEING THE MAIN CLINICAL SYMPTOM TERMINATING THREE DAYS AFTER ADMISSION IN SUDDEN DEATH. TUBERCULAR DISEASE OF BOTH SUPRARENAL CAPSULES. OBSOLETE TUBERCLE IN LUNG WITH CALCAREOUS BRONCHIAL GLANDS.

UNDER THE CARE OF F. W. MOTT, M.D., F.R.S.
Physician to Charing Cross Hospital.

REPORTED BY JOSEPH EVANS, M.B., B.Sc.

THIS patient was sent in by Dr. Galloway as a possible case of tabes with gastric crisis. The patient complains of loss of weight, twitchings in legs, sickness in the morning.

Was well up to June 1903—seven months ago. Then noticed that he always felt tired, continued his work though with difficulty; he could not take his food; by doctor's orders he took oatmeal stout, syrup of phosphates and malt extract. He could not eat meat and had no appetite for ordinary food. Says he had very little but a glassful of egg and milk three times a day.

This condition lasted till six weeks ago, during which time the patient had been steadily losing weight. Loss of weight, 56 lbs. Six weeks ago he noticed twitchings of legs; these came on at night whether asleep or awake. These movements were intermittent, each attack lasting "about half a minute." They began in the feet and then "ran up the leg with a sort of jerk," never noticed them during the day time while at work. These twitchings are painless and are still complained of. About same time as onset of twitching patient began to vomit on rising in the morning; vomiting not preceded by nausea—occurring three or four mornings a week, occasionally during the day, also after meals. During the last week patient has sometimes vomited more than once in the day.

The morning vomit only amounted, he says, to two or three tablespoonfuls; if occurring later in day, it may amount to a

quart. The vomit is described as whitish and frothy, sometimes greenish; does not remember to have previously eaten green food.

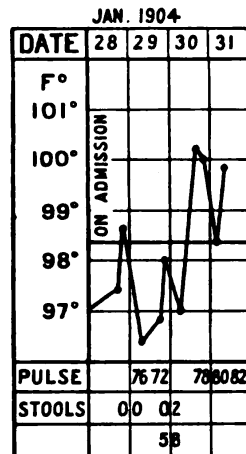
(The vomiting is said to occur more particularly after fluids.)

Previous History.—Never been ill till three years ago, when he had influenza; was in bed a fortnight; no after-effects noticed. Syphilis denied.

Family History.—Father died at 60; cause of death unknown. Mother alive, 75; has "something the matter with her liver." Wife, alive and well, Eight children all alive and well.

General Condition.—Build good; fair nutrition; does not look ill; no appetite; bowels regular; sleeps well; tongue clean; no cough; intelligence and memory good.

Habits.—Teetotaler till six months ago (*vide* above). Smoked till six months ago, three or four pipes of shag daily.



PHYSICAL EXAMINATION.

Alimentary System.—Tongue clean; teeth fair; throat normal; (?) stomach slightly dilated; no tenderness or tumour felt in abdomen; liver not enlarged; no hæmatemesis; no melæna; bowels regular.

Cutaneous System.—No pigmentation was discovered around the nipples, on the genital organs, or at points where there was pressure, nor was there any abnormal pigmented appearance elsewhere on the body or the mucous membranes.

Respiratory System.—No cough; voice very husky; lungs marked emphysema, nothing else noted.

Cardio-vascular System.—*Heart:* Apex beat not felt; sounds normal, heard with difficulty. *Pulse:* Eighty, soft, regular, fair tension, artery not thickened.

Genito-urinary System.—*Urine*: Pale, clear, 1017, acid, no albumen, no sugar, no difficulty or abnormality of micturition.

Nervous System.—Pupils equal, react normally; no loss of power in any part of body; no abnormal sensation in any part of body; knee jerks present; no crises; no squint.

January 29. Vomited 16 ozs. this morning; vomit looks and smells like tea; had no solids for breakfast, only one and a half cups of tea, complains of thirst. Slight cloud of albumen in the urine.

January 31. At six o'clock he was talking to the nurse, having felt and slept better (without drugs) during the night. Just after seven o'clock it was observed by the night sister that he was sleeping peacefully. At seven-thirty nurse heard a little noise of gurgling, and he was found gasping, very cyanosed and cold. He had had his breakfast a little after six o'clock; it was noticed that he had vomited in the porringer the tea and small quantity of bread and butter of which he had partaken about one hour previously. The house physician was sent for immediately as the nurses felt sure he was dying, but before he arrived, although he came immediately, it was found that he was dead.

At the autopsy both suprarenal bodies were found to be caseous throughout. The only other signs of tubercle discovered were some pleuritic adhesions and several calcareous bronchial glands.

DYSENTERY IN THE LONDON COUNTY ASYLUMS — A CRITICISM.

BY J. P. CANDLER, M.A., M.B.(CANTAB.), D.P.H.

Assistant Pathologist to the London County Asylums.

IN the following pages I have endeavoured to briefly criticise some of the most important features in connection with dysentery in the London County Asylums.

It is certain that for years this disease has been very prevalent among the insane, and it is equally certain that no attention of serious moment was given to it by the governing authorities of the London County Asylums until the appointment of Dr. F. W. Mott as Pathologist. At his suggestion a very exhaustive inquiry was commenced, in which he was assisted by Dr. H. E. Durham.

The result of their investigations appeared in the form of a report presented in May, 1900, in which they stated the conclusions at which they had arrived. The most important of these were as follows:—

(1) That in their opinion dysentery was infectious and preventable.

(2) That in its clinical manifestations and pathological appearances it was practically identical with dysentery of tropical climates, although bacteriological confirmation in support of this view was not yet to be obtained.

(3) That the disease was communicated from the sick to the healthy chiefly, if not solely, through the medium of the evacuations.

(4) That the spread of the infection was mainly due to the absence of proper isolation; to the injudicious transfer of cases from one ward to another; to the want of strict cleanliness on the part of the attendants, who in the majority of cases had little or no knowledge of the nursing of infectious diseases; to the imperfect cleansing of contaminated articles; added to which, the dirty habits of the

insane, the difficulty of keeping them in a state of cleanliness, the size of the dormitories, and the general overcrowding which existed in most asylums, had increased the task which had been imposed upon the Medical Superintendents of the various asylums.

(5) That the disease was not limited to the insane, but was liable to attack those in attendance upon them, and also occurred from time to time sporadically outside asylums; the clinical features in these cases being identical with those found in the insane.

(6) That the supposition that the disease was of a purely neurotic origin, and dependent *per se* upon degeneration of nerve centres, was based on purely hypothetical grounds, and was unsupported by evidence.

(7) That in their opinion, nothing short of strict isolation of all affected and suspicious cases, combined with effective and efficient nursing, and methods of sanitation such as were practised in general hospitals, would be likely to cause a reduction in the incidence of the disease.

Finally, a list of recommendations was appended which it was hoped would prove of service to medical officers in their attempts to eradicate the disease.

Such, then, is the brief summary of the main features of the report which was handed to the Asylums Committee of the London County Council, and accepted practically unanimously by the leading medical authorities of the country. The theory of the infectious nature of the disease had the support of all prominent bacteriologists and pathologists.

A leading article in the *British Medical Journal* of April 6, 1901, stated: "Some excuse is possible for the non-appreciation . . . of the infective and probably truly dysenteric character of the colitis prevailing in these Asylums. The continuance of this excuse is now impossible, nor will it be excusable if arrangements are not made for the keeping at each Asylum of an accurate and complete record of all cases of diarrhoea, in order that the extent of the mischief may be properly gauged. . . . Even if it be open to dispute whether the prevailing colitis

is really dysentery, no practical administrator will venture to deny that all patients suffering from this intractable disease must in future be strictly isolated, that the transfers of patients from ward to ward must be strictly restricted in view of possible infection, and that all soiled linen, bedding, etc., must be regarded as infective and treated accordingly. . . . It must of course be admitted that the difficulties in avoiding faecal contamination and infection among lunatics are exceptionally great. The efforts must, therefore, be on a correspondingly large scale. Every detail must be reorganised, attendants must be specially trained for the purpose, and greater personal supervision, medical, sanitary and nursing, must be exercised."

Again, in March, 1902, the same Journal states: "It appears to be now generally agreed that the colitis in Asylums is an infective disease, whether in all cases identical with true dysentery or not. This being agreed, the importance of extreme cleanliness in dealing with diarrhoeal cases in Asylums will be admitted, as also the necessity of not transferring such cases from one ward to another, unless the latter be a special isolation ward. . . . Since the report to the London County Council was issued, the statistics show considerable improvement, and it is clear that the precautionary measures which have been carried out have already had a most beneficial effect on the prevalence of the disease."

At a meeting of the Epidemiological Society of London on December 13, 1901, a paper was read by Dr. Mott, entitled "Dysentery in Asylums," in which the whole subject is carefully reviewed. At the conclusion of the paper the President (Sir Patrick Manson) remarked upon the overwhelming evidence in favour of the prevalence of dysentery in asylums, and questioned the desirability of building vast asylums in which large numbers of sick persons were aggregated together. He also considered that strict discipline of attendants was most essential to proper administration, and that the notification of dysentery should be insisted upon (*vide Transactions of the Epidemiological Society of London*, N.S., vol. xxi., 1901-2).

Since the above report was issued, several papers have been written, mainly bearing on the bacteriology of the disease, all of which tend to confirm the theory of its infectious nature; the only publication, so far as I am aware, which has endeavoured to disparage the views of Drs. Mott and Durham, without offering any new suggestions, being a paper by Dr. Bernard Knobel on the "Etiology of Asylum Dysentery," which appeared in the *Journal of Mental Science*, April, 1906, and to some of whose criticisms I shall have occasion to refer.

Observations on the bacteriology of dysentery.—The theory which was originally propounded that dysentery was due to the action of a specific amoeba has within recent years lost many of its supporters. The failure to obtain the specific amoeba in some cases of undoubted dysentery, as well as its discovery in the evacuations of healthy individuals, has been mainly responsible for this defection; in addition, a large number of cases of undoubted bacillary infection have been discovered. That an amœbic type of dysentery does exist, however, is still claimed by some, the points produced in its favour being that in cases where the amoeba can be recovered from the stools and from the liver abscess which may supervene on protracted cases, the serum reaction with Shiga's bacillus cannot be obtained.

Bacilli in relation to Dysentery.—The discovery of a bacillary form of dysentery is mainly due to the researches of Shiga, Kruse, Flexner, and their pupils.

Shiga, in 1897-1898, isolated from a number of cases of epidemic dysentery in Japan, a bacillus which he obtained from cultivation from the dejecta, from the intestinal walls and from the mesenteric glands. The bacillus isolated by him, while being considered to belong to the colon-typhoid group, yet possessed characteristic properties by which it could be distinguished from the other members of this group. It was regarded as the cause of dysentery in Japan. Similar results were obtained by Flexner in 1899, in cases of dysentery occurring among the American troops in Manila, and also by Kruse in an outbreak of dysentery in Laar in Germany. In addition, the two latter observers

have isolated bacilli apparently belonging to the same group of organisms from cases of dysentery occurring in asylums.

Durham in this country in 1899, working at the Claybury laboratory, isolated a minute micrococcus which had hitherto not been described, from seven cases of asylum dysentery, while he failed to find it in three cases which were not affected with dysentery, and claims in some subsequent experiments in the Cambridge laboratories to have produced lesions of the colon in two animals experimented upon.

The recent researches of Eyre upon the etiology of asylum dysentery published in the *British Medical Journal* of April 30, 1904, are of great importance, in as much as he was the first in this country to isolate from cases of asylum dysentery an organism presenting characteristics identical with that of Shiga's bacillus. He states in his summary, the number of cases he had an opportunity of investigating were "too few to admit of any generalisation as to the etiology of asylum dysentery, but the following statements seem to be quite warranted by the facts observed.

"(1) That a bacillus identical with the *Bacillus dysenteriae* described by Shiga as the cause of acute dysentery in Japan, can be isolated from the stools of many cases of asylum dysentery.

"(2) That the blood serum of these cases of asylum dysentery possesses a specific agglutinative action when tested against the *Bacillus dysenteriae* isolated from the stools of other similar cases, and also against other strains of the *Bacillus dysenteriae* isolated from cases of dysentery in tropical countries."

Eyre was unable to find the presence of the micrococcus described by Durham.

The toxigenic properties of the various strains of the *B. dysenteriae*, notably those of Shiga, Kruse and Eyre, have been tested by Todd, of the Lister Institute of Preventive Medicine (*Journal of Hygiene*, vol. iv., 1904). From alkaline broth cultures of the *B. dysenteriae* of Kruse he was able to obtain a soluble toxin, to which the horse and the rabbit were found to be very susceptible. The serum of an

immunised horse was found to contain a powerful anti-toxin, capable of neutralising the effects of the injection of the toxin. The bacillus of Shiga and also the strains isolated by Eyre from cases of asylum dysentery were found to possess a toxin, the effects of which could be neutralised by the serum of the horse immunised against the *B. dysenteriae* of Kruse. This similarity of action is alluded to by Todd as a strong point in favour of the identity of the strains above mentioned. Rabbits injected with a lethal dose of the toxin developed diarrhoea and paralysis of the limbs; there was a rapid loss of weight, and death in the course of a few days. At the autopsy the large intestine was found to contain slimy fluid; the mucous membrane congested, and small hæmorrhages were present; there was also congestion of, and occasionally small hæmorrhages into, the lung tissue.

Quite recently a very valuable contribution has been supplied by Dr. Saundby, Professor of Medicine of the University of Birmingham (*British Medical Journal*, June 9, 1906), in which he describes a case of sporadic dysentery which came under his care in August, 1905, and from which an organism similar to Shiga's bacillus was isolated.

The discovery of a micro-organism of the Shiga type in a case totally unconnected with asylums is of great importance. In this connection a remark of Flexner in the *Therapeutic Gazette* of April 15, 1902, is of interest. In it he states: "The evidence now in hand proves a widespread distribution of the *Bacillus dysenteriae*. The studies carried on by us last summer have demonstrated the bacillus as the cause of sporadic dysentery; but what seems more important to us is that the terminal dysentery of chronic Bright's disease is likewise caused by this organism. That these facts are of considerable moment with reference to the question of the spread of dysentery admits of no doubt."

I am of opinion, then, that from the bacteriological standpoint, there is strong and increasing evidence to warrant the assumption that dysentery is of very widespread distribution, and that the consensus of opinion is in favour of a bacillary origin of the disease. Pending,

however, the further elucidation of certain points which are still under dispute, and which relate to slight differences in cultural characteristics and agglutinative reactions in relation to the types described by Flexner, Shiga, Kruse, and Eyre, it is at present impossible to decide whether the disease is caused by the action of one specific micro-organism or group of organisms; nor is it possible to judge whether this *B. dysenteriae*, as it has been named, is in reality a member of the colon typhoid group, or belongs to a distinct species. Neither are we yet in a position to judge whether this particular organism or group of organisms is an inhabitant of the healthy intestine, nor do we know the nature of the environment most suitable for the production of its virulent properties.

The dysentery of temperate and tropical climates.—Some controversy has arisen from time to time as to the relationship which exists between the dysentery of temperate and tropical climates. The opinion of Dr. Mott that the two closely resemble one another in symptoms and anatomical lesions, has the support of all those who are most competent to judge, among them being Sir Patrick Manson, the late Dr. Washbourn, and Dr. H. D. Rolleston. Professor Saundby, in his article on sporadic dysentery to which reference has already been made, remarks: "The opinion that dysentery is only a disease of the tropics is not justified by anything in the history of medicine, and has only been suggested by the believers in ulcerative colitis."

Dysentery of asylums; ulcerative colitis and sporadic dysentery.—It has been held by some that an idiopathic ulceration of the colon of a non-infectious nature can be found both in asylums and occasionally without, which has no etiological relationship with the condition usually described as asylum dysentery, and to which the name *ulcerative colitis* should be given. There is no evidence, so far as I can ascertain, for its justification.

Dr. Gemmel, in 1898, remarked on this attempt at division, and considered that there was no essential difference between these so-called cases of ulcerative colitis and asylum dysentery, and that the distinction between the

two diseases was impossible. He further inferred that the substitution of the term "ulcerative colitis" was responsible for the sudden diminution in the number of cases of dysentery reported by some asylums where dysentery was previously common.

Dr. Mott, in the paper read before the Epidemiological Society, also considered such a division to be inappropriate, and stated that, in his opinion, the form of ulcerative colitis described was true dysentery.

Professor Saundby (*British Medical Journal*, June 9, 1906) quotes the opinion of leading writers on the subject; thus Dr. Sydney Martin, writing in "Bain's Text-book of Medical Practice, 1905," states: "Ulcerative colitis is an infective disease of the colon, the cause of which is at present unknown. . . . The morbid anatomy is the same as that of dysentery, and its symptoms are those of an infective diarrhoea. . . . The disease is not infrequently fatal, and the treatment is that of dysentery."

Again he quotes from "Nothnagel's Encyclopædia," in which Dr. H. J. Rolleston says, in reference to ulcerative colitis: "It is unnecessary to give a separate description of the disease, since it may be regarded as dysentery." Dr. Saundby further states that: "After reading the reports of Gemmel and Mott, I cannot doubt that the disease there described is identical with that which has been called 'ulcerative colitis,' and that this is the disease which was formerly called dysentery." Dr. Saundby's report on the cases of sporadic dysentery in England, associated with the presence of Shiga's bacillus, gives further support to the contention of those who believe in the close etiological relationship between the various forms of dysentery.

Evidence in favour of the communicability of the disease.—Let us now briefly consider whether any evidence can be produced as to the mode of occurrence of cases of dysentery in asylums, whether they show any apparent relation to one another, whether there is any relation between the dysentery and diarrhoea cases, and, in general, whether the disease appears capable of communicability from one patient to another. Since the recommendations

of Drs. Mott and Durham were published, a weekly return of all the cases of dysentery and diarrhoea occurring at the various London County asylums has been made. These have been forwarded to the Pathological Laboratory of the London County Asylums, where tabulated records have been kept. These records I have carefully examined, and from them have drawn the following conclusions :—

(1) *Ward incidence*.—In an asylum from which but little dysentery and diarrhoea are reported, when a number of cases do arise, they are almost always confined to one or two particular wards, with but few scattered cases. As an example, let us take Cane Hill Asylum. This institution reports comparatively few cases of bowel disturbance.

Male side.—In the year 1901-02, only 1 case of dysentery was reported ; in 1902-03, 15 cases were reported, this number being made up by 12 cases occurring in the first three months. Of these 12 cases Ward A1 contributed 7, and Ward B1, 2. Later on in the year another case occurred in Ward A1—that is to say, 10 out of the 15 cases were confined to two wards.

In the following year (1903-04) only 1 case was reported, but for the year 1904-05 the number increased to 21. The outbreak commenced in May, 1904, when 9 cases were returned, 7 coming from Ward A1. No fresh cases occurred during the next two months, but during August and September 9 further cases were reported, Ward A1 contributing 5 and Ward A2, 3 cases. Moreover, during January, 1905, 20 cases of diarrhoea (out of a total of 28 for the year) occurred in these two wards, and were attributed to dietetic causes. Thus during the year, out of a total of 21 cases of dysentery, Ward A1 contributed 12 and Ward A2, 6. The diarrhoea cases were, for the greater part, confined to these two wards.

Females.—The female side has been practically free from dysentery, but even the few cases which have been reported have been confined to particular wards. In the year 1903-04, 4 cases were reported. Of these, Ward B1 contributed 3. In 1904-05, 5 cases were reported, Ward A1 contributing 3 and Ward J2, 2 cases. In both years the

cases were practically reported together or shortly following one another.

Horton Asylum (Males).—In 1904-05 the number of dysentery cases reported increased to 7. Ward 9 contributed 4 cases and Ward 8, 3 cases.

(Females).—In 1904-05, 13 cases were reported. Ward K contributed 7 and Wards A, D and B, 2 cases each.

Horton Manor Asylum. Female cases.—In 1902-03, 14 cases were reported. Ward A1 = 6; Ward B, = 5. 1903-1904, 8 cases were reported. Ward A1 = 0; Ward B1 = 5. 1904-05, 8 cases were reported. Ward A1 = 0; Ward B1 = 6.

(2) In asylums which have reported an appreciable amount of dysentery, the cases affect a greater number of wards, and in many instances a similar ward incidence can be noticed, but even where this is not found, the cases appear in groups of two or three in the same ward, reported either together or closely following one another. The following are but a few of the numerous instances of this particular grouping.

Claybury Asylum (Males).—Seven dysentery cases were reported in August, 1904: 4 came from Ward M, and 3 from Ward O.

Females.—Fifty-seven cases were reported during 1904-05. Nine came from Ward D1, and also 7 cases of diarrhoea. The disease, however, was practically endemic in character on the female side, occurring in little groups of two or three cases in various wards, these being reported together or closely following one another.

Hanwell Asylum (Males).—1904-05. In the 16th Annual Report of the Asylums Committee, page 101, I find the following note:—

“The improvement on the returns of the previous years noted in the report of last year has not been maintained, and the dysentery and diarrhoea cases have greatly increased in number. Ward 20 contributed 9 cases of dysentery and 12 of diarrhoea, and Infirmary 5 cases of dysentery and 6 of diarrhoea. Without exception all the dysentery cases occurred in groups of two, three or more cases in the various wards, and were reported together or closely following one

another. One case of dysentery and 1 of diarrhoea have been reported from the male staff."

Bexley Asylum (Males. 1904-05). Ward K contributed about one-half of the dysentery and diarrhoea cases, the remainder being spread about the asylum.

Further striking proof of ward incidence can be found by reference to Dr. Mott's paper "Dysentery in Asylums," reprinted from the *Transactions of the Epidemiological Society*, 1901-02. Reference is here made (p. 20) to an outbreak in a new temporary ward at Colney Hatch, 10 patients being affected, 8 of which occupied adjoining beds. Also to an outbreak in a private asylum which, commencing in an atypical case, spread to patients in adjacent single rooms, affected a nurse, who died, and at whose autopsy acute dysenteric affection of the bowel was found. Also to an outbreak at Hanwell, 18 cases being reported in August, 1901, as against *nil* in July. The majority of the cases came from Ward 20 (10 out of the 18 cases). Three cases of diarrhoea also came from this ward. The only male attendant reported as suffering from dysentery in all the asylums during the preceding nine months came from this ward. From September to November, 1901, 4 male cases of dysentery were reported from Ward 20.

Recurrent cases of dysentery.—A very striking case is mentioned (p. 30) in the same paper, in which two laundry-maids occupying a two-bedded room were attacked with dysentery. It is mentioned as illustrating infection of a healthy person by a recurrent case, the disease in both being similar in clinical characters to that affecting the insane. The case is so important that I will narrate it here, calling the three maids who figure in the story A, B and C respectively.

Case 1.

A (Ward 20) sleeps in a two-bedded room with B, over the laundry.

A began to suffer with diarrhoea and abdominal pains on April 16, 1901. She remained "on duty" for a week, although the diarrhoea did not stop. On April 23, she was so ill that she applied for medical treatment. She was then found to be suffering from severe diarrhoea, with both blood and slime motions.

She was at once isolated in the "hospital," with several other patients who were suffering from a similar condition. After being in the "hospital" for a fortnight she returned "on duty" cured.

B, who slept in the same room, did not develop symptoms of colitis.

A remained free from "colitis" till December 11, 1901, when diarrhœa and abdominal pain again occurred. There was blood and slime in the motions on December 13. On December 14, she first came under medical observation, and was found to have "recurrent colitis."

During the whole of her second illness A has been sleeping in the same two-bedded room with C, in which A developed her first attack.

A is still under treatment (December 16, 1901), for diarrhœa, with blood and slime in motions and abdominal pain.

Case 2.

C (Ward 20), sleeps in the same two-bedded room with A.

On December 14, 1901, when A was found to have "colitis," was ordered not to sleep in the same room.

On the night of the 14th she slept "at home," and on the 15th in a three-bedded room with two nurses in the temporary buildings. On the morning of the 16th she became ill with vomiting, abdominal pain and diarrhœa. While "at home" she noticed some blood in the motions.

She first came under medical observation on December 16, and has been isolated with A in the nurses' block.

The recurrence of dysenteric attacks has been commented upon by Dr. Gemmel, who states: "I have known many instances of patients being attacked several times, the attacks being separated by long intervals; a feature also to be noted in this connection is that those who have once had it (*i.e.*, dysentery) are often the first to feel the influence of a fresh outbreak."

Furthermore, the evidence afforded by the study of the various reports on asylum dysentery, and the weekly returns of the London County Asylums, points strongly to the occurrence of ward incidence and also to the danger of recurrent cases, for in addition to outside evidence, I find on looking through the statistics of the London County Asylums, that there are numerous instances

of recurrent cases, and often the recurrence of dysentery in a particular individual is synchronous with the failing of others in the same ward, who had hitherto been free from dysentery.

(4) *Dysentery and diarrhoea*.—The past few reports of the pathologist have called attention to the importance of immediate treatment and isolation of all cases of diarrhoea, for the following reasons.

(a) The cases of diarrhoea show the same tendency to affect one or more wards in particular, as do the cases of dysentery. A number of cases are reported from one ward and ascribed to dietetic causes, which should really set up cases generally throughout the asylum, as the food is exactly similar for all, except those under medical treatment.

(b) Many cases are returned first as diarrhoea, but after a time are reported as dysentery, which in some cases has proved fatal.

(c) Cases have been reported as merely "diarrhoea," and death has ensued, and at the autopsy, typical dysenteric lesions have been found.

(d) Cases with typical dysenteric lesions have been found at the autopsy, which have not been reported, and apparently not diagnosed during life.

The importance of these precautions cannot be overestimated. In the history of other diseases of an infectious nature disastrous results have followed from failure to detect the mild atypical and latent cases. This has occurred in the history of enteric fever, plague and cholera.

The danger which these latent and atypical cases provide for a community is well exemplified by some recent investigations by Dr. Koch (*British Medical Journal*, 1903) during an epidemic of enteric fever in a small locality named Trier.

He discovered from bacteriological examination of the faeces of undoubted and suspicious cases, as well as of those who had been living in contact with them, that instead of having to deal with only eight cases, which had been

notified by the local medical authorities, seventy-two persons were actually suffering from typhoid, either in a typical or atypical form. Rigid measures of isolation and disinfection sufficed to rid the locality of typhoid fever within the space of three months.

Ward and asylum transfers.—It is impossible with the present system of notification to show how far the transference of cases, which have suffered with dysentery, from one ward to another, or from one asylum to another, has been responsible for the spread of the disease; yet, there is every reason to believe that such a system is fraught with danger. The possible evils which may result have been dealt with at length by Dr. Mott ("Archives of Neurology," vol. ii., p. 761), and the danger is fully illustrated by the history of the recurrent cases to which I have previously referred.

Dr. Knobel has endeavoured to negative this theory, and suggests that the infinite labour and careful observations of the pathologist to the London County Asylums on the subject of transfers, is of little moment in the light of recent investigations.

Without wishing to detract from the value of Dr. Knobel's paper, I think that even now the balance of opinion is in favour of the theory of transfers. In dealing with the question of asylum transfers, I would like to quote the opinions of other authorities on the subject.

Dr. Taylor, the medical superintendent of East Sussex Asylum, Hellingly, in his report for the year ending March, 1905, states that there have been two outbreaks of dysentery during the year; one, slight, was confined to the female side; all were transfers from other asylums.

The other outbreak, more severe in character, was confined mainly to two wards. Of the fourteen patients attacked, ten were transfers from other asylums, and only four were new cases.

He proceeds: "There is no doubt in my mind that this disease was imported from other asylums. Unfortunately dysentery is a disease which is constantly liable to relapse, and often a patient who has suffered from previous attacks.

will have a relapse with but slight symptoms. It is these cases which spread the disease, and they are peculiarly difficult to detect. The only way to eradicate it appears to be permanent isolation of any case which has once been attacked, and it is very desirable in my opinion that in building asylums a detached block on each side should be provided for these patients. Many of them will remain well for months, and are quite capable of work, but one never knows when the relapses will occur. Its incidence and rapid spread in new asylums seems to be easily explained by the number of susceptible people who are brought together often for the first time, and mixed with transfers from old asylums."

Dr. Stansfield, the present medical superintendent at Bexley Asylum, stated at the discussion on Dr. Mott's paper before the Epidemiological Society (*British Medical Journal*, 1902, p. 397) "That patients are constantly transferred from overcrowded asylums, and that those newly opened were thus filled. If any such transfers were suffering from a latent form of the disease they would develop it sooner or later. Thus at Bexley, where the sanitary arrangements were perfect, dysentery broke out within three years of the opening of the asylum, the first cases being invariably transfers."

Dr. Stansfield, however, appears either to have forgotten this statement, or has altered his opinion very considerably, for in the Sixteenth Annual Report of the London County Asylums, he writes with respect to dysentery: "A former assistant medical officer of this asylum, Dr. Knobel, has devoted himself to the close study of this disease, and has analysed and tabulated the cases that have occurred. He has produced a number of most interesting and instructive diagrams and charts which I recently had the opportunity of exhibiting to the Sub-Committee. The results all tend to refute the ideas as to the great infectivity and mode of propagation of the disease which have been put forward by Dr. Mott.

In Dr. Mott's paper "Dysentery in Asylums" he states: "When I was appointed Pathologist to the London

County Asylums I soon recognised that dysentery, or, as it was called, "colitis" was very prevalent at Claybury, and that numbers of people were dying of a preventable disease which had assumed an epidemic form." He does not, however, so far as I am aware, make any remark upon the "great infectivity" of the disease.

Disturbance of the subsoil in respect to outbreaks of dysentery.—In his attempt to explain the reason for the outbreak of dysentery in new asylums, Dr. Knobel considers the effect of the disturbance of the subsoil as being a possible factor in the production of dysentery. In support of this theory, he states: "It is well known that the disease frequently breaks out in new asylums shortly after occupation. This has been the case in most of the recent asylums, although the modern institutions are built with every regard for perfect hygiene. It occurred at Claybury, at Bexley, the Manor, and Horton Asylums, the four latest additions to the London County Asylums. In these dysentery appeared within a few months of the opening of the asylum."

I hardly think that the question of the disturbance of the subsoil in the case of Bexley need be considered, as the present medical superintendent has already expressed his opinion that the outbreak at Bexley was due to transfers. Also Dr. Taylor, the medical superintendent of the new East Sussex Asylum at Hellingly, has stated that the majority of the patients affected by the two outbreaks of the disease at this asylum, were transfers.

In respect to the part played by the disturbance of the subsoil in the causation of dysentery, much further investigation will be required before any definite statement can be made, but it certainly does not receive any support from the fact that epileptics who as shewn by the Claybury death returns (*vide* Table I.) are as prone to the disease as patients suffering from other forms of mental disorder) have not contracted the disease at the Epileptic Colony, although they are constantly disturbing the subsoil in their agricultural labours, and also are residing in a new asylum, which, according to Dr. Knobel, is in itself a factor in determining the outbreak of dysentery.

I am given to understand that an elaborate system of notification of transfers, and subsequent careful treatment of all cases which are liable to set up infection, is in vogue at the colony, and I am of the opinion, in spite of Dr. Knobel's assertions, that this may explain the freedom of that institution from dysentery.

Moreover, the total number of patients resident at the Epileptic Colony is limited to between three and four hundred; consequently in this asylum the crowding together of large numbers of patients in wards of extensive dimensions does not exist to anything like the extent that it does in the older and more densely populated asylums.

Nerve degeneration and dysentery.—The supporters of the theory that asylum dysentery is a form of ulcerative colitis and not infectious, have suggested that the intestinal condition found among the insane is due to trophic nerve changes.

Dr. Claye Shaw, while owning that the condition is of bacterial origin, stated in a discussion on Dr. Mott's report: "That there was at least a possibility of another interpretation for what I take to be a condition inseparable from some states of chronic insanity, viz., a degeneration of the tissues of the intestinal coat (perhaps beginning in Meissner's plexus) leading to ulceration, with diarrhoea or dysentery."

So far as I am aware no such degenerative changes have been found at present by any observers; though they have been carefully searched for by Dr. Mott, upon the lines suggested by Dr. Claye Shaw, and I am unable to find any grounds for the belief that dysentery can be caused by nerve degeneration *per se*, except such as are based on pure hypothesis; against this theory we have the following facts:—

(1) That the disease is not by any means limited to the insane, but attacks attendants and medical officers, and also occurs sporadically outside asylums.

(2) That it attacks all classes of the insane irrespective of age, sex, form of mental disorder, or length of residence in the asylum, though it seems to show a preference per-

haps for those who are old and feeble (*vide* Tables I., II., and III.).

(3) That it is not confined to cases showing gross degenerative nerve changes, such as general paralytics or tabetic cases with general paralysis; and cases of this nature which have shown the most marked changes at autopsy and subsequently by microscopic examination have not suffered from dysentery.

(4) That at Claybury Hall, where 25 per cent. of the patients suffer from general paralysis, there has not been a single case of dysentery reported since the opening of the building.

(5) That if the disease were due purely to nerve degeneration the cases would occur scattered irregularly throughout the various wards without any marked tendency to grouping which is so repeatedly found, and to which attention has been drawn.

(6) That the disease is relatively more common in females, among whom the mortality from gross organic nerve changes, such as general paralysis, is less than among the males.

I have recently been able to examine the records of the deaths with dysenteric lesions which have occurred at Claybury Asylum during the last few years (September, 1898, to March, 1906) (*vide* Table I.).

The most interesting points noted were : (1) Out of a total of 237 deaths with dysenteric lesions 162 were females and 75 were males, *i.e.*, there were twice as many deaths among the females, a fact which, in my opinion, is more easily explained by their greater liability to infection, owing to the difficulty experienced in keeping them in a cleanly and dry condition, than by assuming that nerve degeneration is totally responsible. Another factor to which I am inclined to attach considerable importance, is the greater proneness of females to constipation, in the wake of which fæcal sapræmia, congestion and erosions of the intestinal mucous membrane are so liable to follow, thereby rendering the large intestine especially more vulnerable to microbial invasion.

(2) That reference to the age of the patients at the time of their death shows that no special decade appears to be specially selected (*vide* Table II.).

(3) That the disease is liable to attack patients suffering from all forms of insanity without any marked predilection for any particular kind.

(4) That it may attack patients, not only after years of residence, but is also prone to kill them within a few months of admission.

Out of the 237 cases examined, 47, or 20 per cent., died with dysenteric lesions within six months of their admission to the asylum. Assuming that the dysenteric affection was caused by nerve degeneration, it is surely rather remarkable that so large a percentage of the cases should have been attacked within so short a time of admission to the asylum.

(3) Lastly, I have taken the length of residence in Claybury Asylum of females who have suffered respectively from puerperal, epileptic and alcoholic types of insanity, and in whom dysenteric lesions have been found at the autopsy (*vide* Table III.). The period of years examined was the same as previously mentioned (*viz.*, September, 1898, to March, 1906), and although, in some instances, in all three types of insanity, the duration of life in the asylum has been spread over some few years, yet it will be found that those who have suffered from alcoholic insanity have been in some cases carried off after a very short residence (in some instances measured by weeks), whilst those suffering from puerperal and epileptic insanity do not show this liability to infection to anything like so noticeable a degree, which suggests that the presence of gastric and intestinal catarrh, so prevalent in alcoholic subjects, has rendered their tissues more susceptible to infection.

Out of 15 cases of alcoholic insanity, 5 died within seven months from the time of admission; and one of these within one month, dysenteric lesions being found at the autopsy. Dr. Mott informs me that he has had a very considerable number of cases of severe alcoholic polyneuritis in Charing Cross Hospital, but he has never seen it associated with dysentery or colitis. In the cases of puerperal

and epileptic insanity no death, associated with dysentery, occurred before one year had elapsed from the time of admission.

No one, I am sure, wishes to deny that the insane by reason of their diminished vitality are rendered more liable to the onset of dysentery and other diseases, whatever their nature ; but the supporters of the theory of nerve degeneration must either believe in their own hearts that asylum dysentery is infectious, or not. If they believe the latter, they must bring, in support of their own theory, evidence that is based on more than mere hypothesis ; if, in the former, then surely there is all the greater need to protect those who by reason of their infirmity and surroundings are rendered so extremely vulnerable to the attack of this disease.

Some of Dr. Knobel's assumptions are obviously at fault, and I hardly think that he really means all that his paper implies. He has suggested that because the Pathological Laboratory is situated at Claybury, this institution before all other asylums should show the fruits of Dr. Mott's recommendations.

In reply to this I would suggest that the figures he quotes concerning the number of cases reported from Claybury alone, from 1901-1904, do show a very material decrease in the incidence of the disease (*vide* Tables IV. and V.). But, further, he must surely be aware that whatever Dr. Mott may recommend with regard to isolation of dysentery and diarrhoea cases, he has no more control over the internal management of this asylum and the disposal of these cases than he has over the other asylums of the London County Council ; otherwise he would be able to take the credit for the present satisfactory condition reported as regards dysentery from Banstead Asylum, as being the outcome of his own endeavours.

So, too, I am of opinion that Dr. Knobel has rather underrated the improvement in the condition of the asylums as regards dysentery (*vide* Table IV.). Taken collectively the returns for the past few years have dropped, but for the year 1905 to 1906 they show a tendency to rise again.

Where is the cause of this increase to be found? Banstead reports no cases, Colney Hatch has improved considerably, the Horton Asylums report but few; Claybury returns remain about the same, Hanwell may show a slightly increased number, but Bexley reports an abnormally high number of dysentery cases, and were it not for this asylum the dysentery returns for 1906 for the asylums collectively would show a further improvement.

For the year 1904-1905, 95 male and 136 female cases were reported from all the asylums, making a total number of 231 cases, of which Bexley contributed 19 male and 28 female cases, making a total of 47. For the following year from the asylums collectively 114 male and 160 female cases were reported, making a total of 274; of these Bexley contributed 63 male and 66 female cases, together totalling 129, or nearly 50 per cent. Thus, if Bexley be eliminated from the statistics, the figures for 1905-1906, in spite of an increased number of cases at Hanwell, would show a diminution from 184 to 145 cases.

But here it must be stated that the reports convey the impression that the personal equation with regard to the conception of dysentery and diarrhoea cases varies for each asylum. While correcting the proofs of this paper I was able to study the reports for the summer months of this year, during which time the returns were rather heavy. At Banstead, in the beginning of June, on the male side, a fatal case of dysentery was reported, the autopsy confirming the diagnosis; following this, a few cases of diarrhoea occurred in the same ward, one of which, as was ascertained later, showed dysenteric lesions at the autopsy, although the return in this case was *slight diarrhoea* and later, *severe diarrhoea*. In September, 26 cases (11 severe) of diarrhoea were reported; these were confined to six wards (M1, 9; H1, 5; H3, 4; K, 4; H2, 3; 5, 1).

Again, on the female side, during September and October, 68 cases of diarrhoea (45 severe) were reported; of these Ward E contributed 45; F, 7; B, 3; R1, 3; R2, 2; C, 5. Two of these cases died in the beginning of September, and the *post-mortem* reports were "ulceration

and gangrene of the colon " and " ulceration of the colon," respectively.

In view of these facts, the question arises whether others amongst these cases may not have been dysentery, and whether other Medical Superintendents would not have placed all the severe cases of diarrhœa under the category of dysentery, for at Bexley I find there are but few cases of diarrhœa reported, whereas the number of dysentery cases appears to be larger than ever.

Moreover, other asylums report but little diarrhœa, and it seems incredible that asylums having similar populations, comprised of people drawn from the same grade of society, should show such variation in their statistics, for I find that one asylum will report more diarrhœa cases in one week than another will report even in one or two years. In the latter instance possibly the cases may have been overlooked; failing this, the condition is one which affords a powerful argument against the theory that dysentery is due to nerve degeneration.

I am well aware of the great difficulty which exists in the differential diagnosis between dysentery and diarrhœa; attention has already been drawn to this by Dr. Mott in his report, and constitutes one of the many weighty arguments he has brought forward for a systematic and thorough isolation and notification of all cases of bowel disturbance, if an attempt is to be made to eradicate dysentery from the asylums, but in view of the variations to which I have already referred, I can hardly believe that the present system of notification shows the true condition of the various asylums with regard to the incidence of dysentery, nor do the efforts which are at present being made to control the disease appear to reach the standard suggested in the recommendations of the Pathologist.

CONCLUSIONS.

From a careful study of the literature relating to asylum dysentery I have come to the following conclusions:—

- (1) That the disease is infectious and preventable.

(2) That it is caused by the action of an organism (or group of organisms) generally known as the *Bacillus dysenteriae*.

(3) That the disease is communicable mainly by contact with the excreta of infected persons and articles contaminated therewith; in this way closely resembling the manner in which enteric fever is spread.

(4) That the disease can attack the sane as well as the insane, and can occur sporadically outside the sphere of asylums, but that it is especially liable to occur when a large number of people of lowered powers of resistance and of uncleanly habits are brought into close association, as occurs in the case of lunatics congregated together in large and over-crowded asylums.

Furthermore, I am of opinion that owing to the lack of adequate accommodation in many of the asylums for the reception of cases of dysentery, the methods of isolation of infected and suspicious cases cannot be carried out in the manner recommended in the report of the pathologist, and there is little possibility of the disease being removed from the asylums unless isolation and its attendant difficulties are combined with systematic bacteriological research.

The scattered distribution of the London County Asylums, and the consequent difficulties of organisation, render this combined work a matter of impossibility, but I believe it would be practicable if it could be reduced to more workable limits.

This, I think, could be effected if it were decided :

(1) To commence an organised investigation extending over a definite period.

(2) To limit the investigation of cases to one particular asylum.

(3) To provide adequate accommodation for prolonged isolation of definite and suspicious cases, including those of diarrhoea, which would be removed immediately upon detection to the isolation block from the main building, and from which would be derived the material for bacteriological research.

This research would be directed to further the elucidation

tion of several matters which are at present the subject of controversy, and to lay the basis for the most thorough and rational treatment of cases of dysentery which can be evolved. It would include :—

(1) The investigation of every case of dysentery and diarrhœa in the asylum.

(2) The search for the causative organism, the earliest date at which it can be detected in the course of the disease, the method whereby the disease is spread, and the length of time a patient may remain infectious after recovery from the attack.

(3) The investigation as to the agglutinative properties of the serum of affected patients.

(4) Research into the possible value of serum-therapy.

As the result of some such systematic and thorough investigation of the disease, confined in the first instance to cases arising in one particular asylum, I believe that a rational system of treatment would be discovered, which would be of benefit both to the individual and to the general community, and which, if successful, could be adopted by the rest of the asylums of the London County Council.

Failing this, I am convinced that the incidence of the disease can be diminished to a very great extent by stringent and prolonged isolation in wards set apart for the purpose, of all cases denoting any signs of bowel disturbance.

The present system of allowing patients who have only just recovered from an attack of dysentery to return at once to a general ward is simply courting disaster.

The term "isolation" denotes far more than the mere detention of a patient during the active phase of the disease ; it embraces other prophylactic measures of equally great importance ; and until this is fully appreciated in the case of dysentery, as it has been already in the case of other infectious diseases, such as enteric fever and the like, there is little prospect that the incidence of the disease will be further diminished, let alone eradicated from the London County Asylums.

TABLE I.—SHOWING THE TYPES OF INSANITY IN WHICH DYSENTERIC LESIONS WERE FOUND AT THE AUTOPSY AT CLAYBURY ASYLUM (SEPTEMBER, 1898, TO MARCH, 1906, INCLUSIVE).

	Females	Males
<i>Mania</i>	27	7
" <i>Senile</i>	8	3
" <i>Epileptic</i>	2	2
" <i>Alcoholic</i>	2	0
" <i>Puerperal</i>	2	—
" <i>With imbecility</i>	2	0
<i>Dementia</i>	8	8
" <i>Senile</i>	23	12
" <i>Alcoholic</i>	13	0
" <i>Epileptic</i>	6	4
" <i>Syphilitic</i>	2	1
<i>Melancholia</i>	27	6
" <i>Epileptic</i>	2	0
" <i>Senile</i>	18	9
" <i>Puerperal</i>	3	—
" <i>With imbecility</i>	2	0
<i>General Paralysis of the Insane</i> ..	15	21
<i>Syphilitic brain disease</i>	0	2
	162	75
Total	237	

TABLE II.—SHOWING THE AGE AT TIME OF DEATH IN CASES ASSOCIATED WITH DYSENTERIC LESIONS, CLAYBURY ASYLUM, SEPTEMBER, 1898, TO MARCH, 1906, INCLUSIVE.

	Females	Males
10 to 19 years	1	0
20 " 29 "	11	6
30 " 39 "	33	13
40 " 49 "	23	12
50 " 59 "	27	18
60 " 69 "	32	15
70 " 79 "	31	10
80 " 89 "	4	1
	162	75
Total	237	

TABLE III.—LENGTH OF RESIDENCE IN CLAYBURY ASYLUM OF FEMALES SUFFERING FROM ALCOHOLIC, PUERPERAL AND EPILEPTIC INSANITY RESPECTIVELY, AND AT WHOSE AUTOPSY DYSENTERIC LESIONS WERE FOUND.

September, 1898, to March, 1906, inclusive.

ALCOHOLIC INSANITY				PUERPERAL INSANITY				EPILEPTIC INSANITY			
No.	Age	Length of residence		No.	Age	Length of residence		No.	Age	Length of residence	
		Years	Months			Years	Months			Years	Months
1	37	—	6	1	34	4	—	1	64	2	—
2	44	—	6½	2	41	6	—	2	22	3	9
3	50	3	—	3	37	3	—	3	15	1	—
4	35	—	3 weeks	4	33	4	6	4	52	1	7
5	44	—	7	5	29	2	—	5	71	6	8
6	75	—	11					6	32	4	2
7	39	—	1					7	34	5	1
8	60	2	7					8	41	4	10
9	54	2	7					9	69	4	8
10	44	5	—					10	66	1	—
11	48	5	—								
12	43	2	9								
13	32	1	1								
14	37	—	6½								
15	—	2	—								

TABLE IV.—INCIDENCE OF DYSENTERY AT THE VARIOUS ASYLUMS.

	1901—1902	1902—1903	1903—1904	1904—1905	1905—1906
Claybury ..	101 (1)	96	91	67	72
Banstead ..	24	45	1	0	0
Bexley ..	34	104	47 (1)	47 (1)	129
Cane Hill ..	6	15	5	26	6
Colney Hatch ..	67	71	46	37	14
Hanwell ..	60 (5)	33 (1)	21	26 (1)	44
Horton ..	Not opened	9	13	20	4
Manor ..	5	13 (1)	8 (1)	8	4
Epileptic Colony ..	..	..	..	1 (?)	1

Note.— Figures in parentheses denote cases among the staff.

DYSENTERY IN THE LONDON COUNTY ASYLUMS 319

TABLE V.—SHOWING DEATHS ASSOCIATED WITH DYSENTERIC LESIONS AT CLAYBURY ASYLUM.

	March 1, 1898, to Feb. 28, 1899	March 1, 1899, to Feb. 28, 1900	March 1, 1900, to Feb. 28, 1901	March 1, 1901, to Feb. 28, 1902	March 1, 1902, to Feb. 28, 1903	March 1, 1903, to Feb. 28, 1904	March 1, 1904, to Feb. 28, 1905	March 1, 1905, to Feb. 28, 1906
Males	22	20	8	10	4	11	4	2
Females	40	35	33	9	16	13	12	17
Total	62	55	41	19	20	24	16	19

DEATHS AT CLAYBURY ASYLUM IN WHICH DYSENTERY WAS THE
PRIMARY CAUSE.

	1898	1899	1900	1901	1902	1903	1904	1905	1906
Males	15	8	2	5	3	9	3	2	
Females	23	16	22	6	8	11	11	15	
Total	38	24	24	11	11	20	14	17	

Note—Dr. Mott's Report was presented to the London County Asylums Committee, May, 1900.

PARAMYOCLONUS MULTIPLEX WITH EPILEPSY
—AFFECTING FOUR MEMBERS OF A FAMILY
—WITH MICROSCOPIC EXAMINATION OF
THE NERVOUS SYSTEM IN A FATAL CASE.

BY F. W. MOTT, M.D., F.R.S.

Family History.—Father healthy, but subject to rheumatism. An old soldier; served in Crimea and India. Mother healthy, but subject to rheumatism. Maternal uncle suffered with epilepsy. Nine children born.

(1) Girl. Died, aged 25, from consumption and spinal disease.

(2) Girl. Had fits at 11, similar to D. M. Died at 27.

(3) Girl. Died 12 months old. Had convulsions.

(4) Girl. Alive, healthy, but not robust. Married at the age of 32. Has had four children. Three alive and healthy.

(5) Girl. Healthy, but not robust. Married, and has one healthy child.

(6) Boy. D. M., at present in Claybury Asylum.

(7) Boy. Aged 23. W. M., died at Wandsworth Infirmary.

(8) Girl. Aged 20. Began about 12 years old to have fits similar to her brothers. She is as helpless, but is not affected mentally.

(9) Girl. Died in infancy.

D. M. Patient is stated to have been a fine healthy child up to the age of 12, when he began to have distinct epileptic fits. The other convulsions came on so gradually that mother is unable to state when they really started, but nearly eight years ago he was so helpless that he had to be removed to Wandsworth Infirmary. Just before that he made a serious attack on his brother and made him insensible for several hours. When asked why? he said: he had annoyed him, but did not seem in the least sorry at his conduct. After two years he seemed better, mentally and physically, and was taken home again. After being

home fourteen days he relapsed, could not be trusted, and had to be sent back again. He was sent to Hanwell, where he attacked some of the patients. Later he was transferred to Leavesden where he attempted suicide, trying to sever the arteries of his wrists with broken plates. He was sent back to Hanwell, where he tried to commit suicide in a similar way. On each occasion he evinced no sorrow at his act, and seemed quite unconcerned.

I came to hear of this case by my attention being called in September, 1899, by Dr. Alexander, to the existence of a curious case of epilepsy at Hanwell. I found that it was a case of paramyoclonus multiplex with epilepsy (this case was briefly referred to in my Croonian Lectures, 1900). I made the following notes:—

D. M. was admitted to Hanwell on account of attempted suicide and epilepsy. Four other members of the family, two males and two females were affected in the same way and the disease commenced at about the same age. A sister died of the disease at the age of 27, there is a sister living at home, and a brother, William, who is at Wandsworth Infirmary. As children they had scarlet fever.

September 20, 1899, I visited Hanwell, and took the following notes of patient. He is an intelligent patient, and apart from the effort of speaking, owing to the involuntary incoördinate jerky spasm of all the muscles of his body, including the face and tongue, he is able to give a very good history of his family, and converse rationally upon other topics. He reached the Fifth Standard in the Board School. The speech is unaffected, except as a result of the spasms, which vary in intensity at different periods of time. Eight days ago he had a fit. He kept an account of the number of fits he had in 1898, and it amounted to thirty in all. They mostly come on at night. After the fit, for three or four days the limbs feel numbed, but the spontaneous choreiform jerking movements are much better. The fits appear to be quite typical of *epilepsia major*. The aura is a feeling of giddiness in the head, which is followed by sudden loss of consciousness, gurgling in the throat, tonic spasm of all the muscles, pallor, redness, and eventually cyanosis and foaming at the mouth. He does not bite the tongue, but sometimes passes water. The tonic spasm lasts about twenty to thirty seconds and passes into clonic spasms, followed by deep sleep for a couple of hours or so. For some days after the fit, when spontaneous jerky muscular spasms are comparatively quiet, he can walk and write much better and perform other voluntary movements aided by an effort of attention. If however, his attention be distracted from what he is doing under the influence of his will power the irregular jerky spasms return. He stands with a wide base, and walks with his legs far apart owing to the incoördinate jerky irregular spasm of the muscles of his legs. These rapid jerky

clonic spasms affect indifferently and with no successive character all the muscles of both the upper and lower limbs, head and neck. Single and not synergic associated groups of muscles are affected by these clonic spasms. The spasms at times continue even when the patient is at rest in bed, but they cease during sleep. Sometimes, he is quite unable to walk, and has to be supported by the attendant. It appears then that he is quite unable to raise one foot from the ground to make progression, on account of losing his equilibrium from irregular spasm of muscles in the resting leg. All the deep reflexes are exaggerated. There is no loss of sensation and no marked loss of sense of position, but he does not know when his big toe is passively flexed or extended in which direction it points. There is an *extensor reflex response on scratching the foot*. In July, 1901, this patient was transferred from Hanwell to Claybury Asylum, where he is still under treatment.

William M., aged 16, on admission to Wandsworth Infirmary. I saw this patient in October, 1900, when he was aged 22, and then made the following notes of his condition. This patient is in a much worse condition than his brother in Hanwell Asylum, as he is now practically bedridden, and has been so since Christmas; last summer, however, he was able to go out in a wheeled chair.

Statement by patient.—He has great difficulty in expressing himself, on account of the jerky spasm of the muscles, which leads to the words after some delay being jerked out and sometimes slurred or cut in two. There is some rigidity in the facial expression, but he is easily moved to tears or laughter. He thinks the fits are becoming more severe and less frequent, his memory is becoming impaired and he has a difficulty in swallowing, owing to the spasm. The lips and tongue are coarsely tremulous.

Description of fits of which he has had one lately.—He knows when the fit is coming on by a cramp in one or both feet, generally the left, gives a cry and then falls down unconscious. Then follows tonic spasm, cyanosis, foaming at the mouth and general clonic spasms; for some time after the fit he suffers with headache. For some days, and sometimes a week before the fit, the myoclonic spasms are much worse. He had a fit a few days ago and since then the spasm has been much less, and this is usually the case. The bowels are generally relaxed before a fit, and he feels irritable and ill-humoured; whereas, after a fit he feels more cheerful and he can swallow his food better. I gave him some milk to drink and he managed to get it down very well. The nurse says that sometimes, preceding a fit, he could not swallow fluid without choking, on account of the muscular spasm. He wrote his name, steadying to some extent his right hand by holding his wrist with the left hand. There is no affection of sensation, no trophic affection of the muscles. He can dorsal flex the foot

although there is a tendency to foot drop (possibly weight of bed-clothes lying in bed). All the deep reflexes are exaggerated, slight foot clonus both sides, no plantar extensor response. Pupils equal, react to light and accommodation. He was intelligent and had reached the sixth standard.

I did not see this patient again, but by the kindness of Dr. Jones I was informed of his death, and through the permission of the superintendent of the Wandsworth Infirmary I was enabled to obtain an autopsy. Unfortunately it was in the warm weather and the patient had been dead twenty-four hours before the examination was made. The patient, who was extremely emaciated, died (July, 1905), of broncho-pneumonia and heart failure, accelerated by status epilepticus.

Post-Mortem Notes.

William M. (paramyoclonus multiplex). July 13. *Post mortem* twenty-four hours after death. Body rather emaciated, physique good, muscles not wasted, good colour. Some foot drop possibly through lying in bed with weight of bed-clothes. Large bedsore over the lower part of sacrum. No other bruises, scars or sores. *Post mortem* decomposition commencing.

Skull.—Thicker and denser than natural.

Dura.—No adhesions. No obvious thickening of pia-arachnoid. Slight excess of sub-arachnoid fluid. Brain very watery and oedematous. Weight $45\frac{1}{2}$ ozs. Weight of cerebellum and pons 7 ozs. Hemispheres, weight of each 18 ozs. Fourth ventricle, ependyma not granular.

Convolutional pattern.—Convolution small, complex. Grey matter rather thinner than natural. Membranes strip in one piece, a good deal owing to oedema. Calcarine fissure ends in vertical fissure of Seitz each side. Parietal development good. Line of Gennari ends within the pole both hemispheres.

Slicing up the brain and cord after preliminary hardening in formalin exhibited no gross lesions, appreciable to the naked eye. The following parts were taken: ascending frontal and ascending parietal for Nissl and Cajal methods. The upper part of the cord and spinal ganglia for Nissl and Weigert method. The ulnar and adductor muscle for Marchi and other methods.

Cardio-vascular system.—Heart flabby, friable and apparently exhibiting early fatty change. No valvular lesion, no atheroma of the aorta.

Lungs.—A few very old adhesions, and scar at right apex of healed obsolescent tubercle. Broncho-pneumonia, bronchitis and emphysema of both lungs with consolidation and commencing gangrenous breaking down of the base of the lower lobe of the right lung.

Liver.—Enlarged, congested, otherwise normal.

Kidneys.—Large, congested. Cortex apparently diminished in thickness, capsule strips readily. Portions of heart and kidney reserved for microscopical examination.

Immediate cause of death.—Broncho-pneumonia. Probably the result of food getting into the bronchi. Cardiac failure.

The tissues were hardened in formol, Müller, and silver solution for Cajal method. It was subsequently found that the tissues were not in a very satisfactory condition, and the results obtained may be partly accounted for by fever, status epilepticus and septic-toxæmia. There are, however, certain changes affecting the Betz cells especially, which were of prolonged standing, and cannot be attributed to immediate *ante-mortem* and *post-mortem* conditions. The peripheral nerves examined by Marchi method showed no change. The spinal cord no defined change, although there were scattered black granules in the white matter. In the grey matter, however, it was noticed that the multipolar anterior horn cells were black either wholly or in part. This was due, probably, to excess of yellow pigment taking up the osmic acid. The amount of pigment seems to depend in normal states upon the age of the individual. As he was a young man it was far more than normal. The kidneys showed either degeneration or accumulation of fat in the epithelium of a great many of the convoluted tubules. The liver showed marked fatty infiltration of the liver cells. The heart showed brown pigmentation and some fine fatty degeneration of the fibres.

Brain and spinal cord.—Tissues hardened in formol and embedded in paraffin sections 5 μ cut and stained by polychrome and eosin to exhibit structure of ganglion cells and glia cell changes. The striking feature about the cortex cerebri was the bright blue staining of the glia and endothelial cell nuclei, and the imperfect dull purple staining of the ganglion cells and their Nuclei. The glia cells are much proliferated, but they are young cells and have not large and numerous branching processes. They can be seen dividing into pairs and groups. The nucleus is deeply stained blue, and the body a pale pink. The ganglion cells are all stained a diffuse dull pinkish purple, indicating a biochemical change. In none of the large Betz cells found at the top of the ascending frontal in great numbers could the Nissl granules be seen in the body of the cell or the dendrons. The whole neuron, including the nucleus, is stained a diffuse purple. The nucleus is visible by the deeper staining of the nucleolus and nuclear membrane. In some of the cells there is a trace of the mosaic pattern by the light yellow of the excess of pigment showing itself between what were originally the spaces of the Nissl granules in some of the cells. Some of the cells, however, are

practically unstainable, and nearly the whole portion of the body of the cell seen in the section is yellow, from the pigmentary degeneration (*vide* fig. 1, plate iii.). Even if the change of the Nissl substance is due to the complications *ante mortem* or *post mortem*, I think there can be no doubt that the pigmentary degeneration of the psychomotor cells cannot be accounted for by such complications immediately preceding death or *post mortem*, and therefore especially as they appear to be limited to the psychomotor cells, may be associated with the myoclonic condition. Moreover, the patient showed no mental deficiency during life, and the symptoms he manifested were, apart from the epilepsy, purely motor. Thus we should not expect to find any marked changes in the pyramidal layers of the cortex.

The changes in the anterior horn cells of the spinal cord were far less obvious (*vide* fig. 2, plate iii.). The processes appear broken off. There is excess of yellow pigmentation and the Nissl granules are indistinct, but the cells differ in staining reaction to those in the cortex, for they do exhibit a proper basophil reaction, whereas the cortical pyramidal cells, and especially the Betz cells show a mixed basophil and acidophil reaction staining a pinkish purple.

Remarks.—This disease was described first by Friedreich in the year 1881. A number of cases have been since recorded. According to Oppenheim ("Lehrbuch der Nervenkrankheiten") the accurate investigation of the nervous system has only once been undertaken. The case was that of Schultze, who, however, obtained negative results throughout.

Unverricht described first the special familiar form of the disease, characterised by association with epilepsy; moreover, in some of his cases the tongue and muscles of deglutition were affected as well as the diaphragm. Cases of this type have also been described by Weiss, Krewer and Sepilli. The fatal case here described and the remaining members of the family affected were all epileptics. It was hereditary probably, for an uncle was said to have suffered with epilepsy. The broncho-pneumonia which killed the patient very probably was occasioned by a myoclonic spasm occurring while swallowing, fluid or food thus entering the respiratory passages.

DESCRIPTION OF PLATE III.

PARAMYOCLONUS.

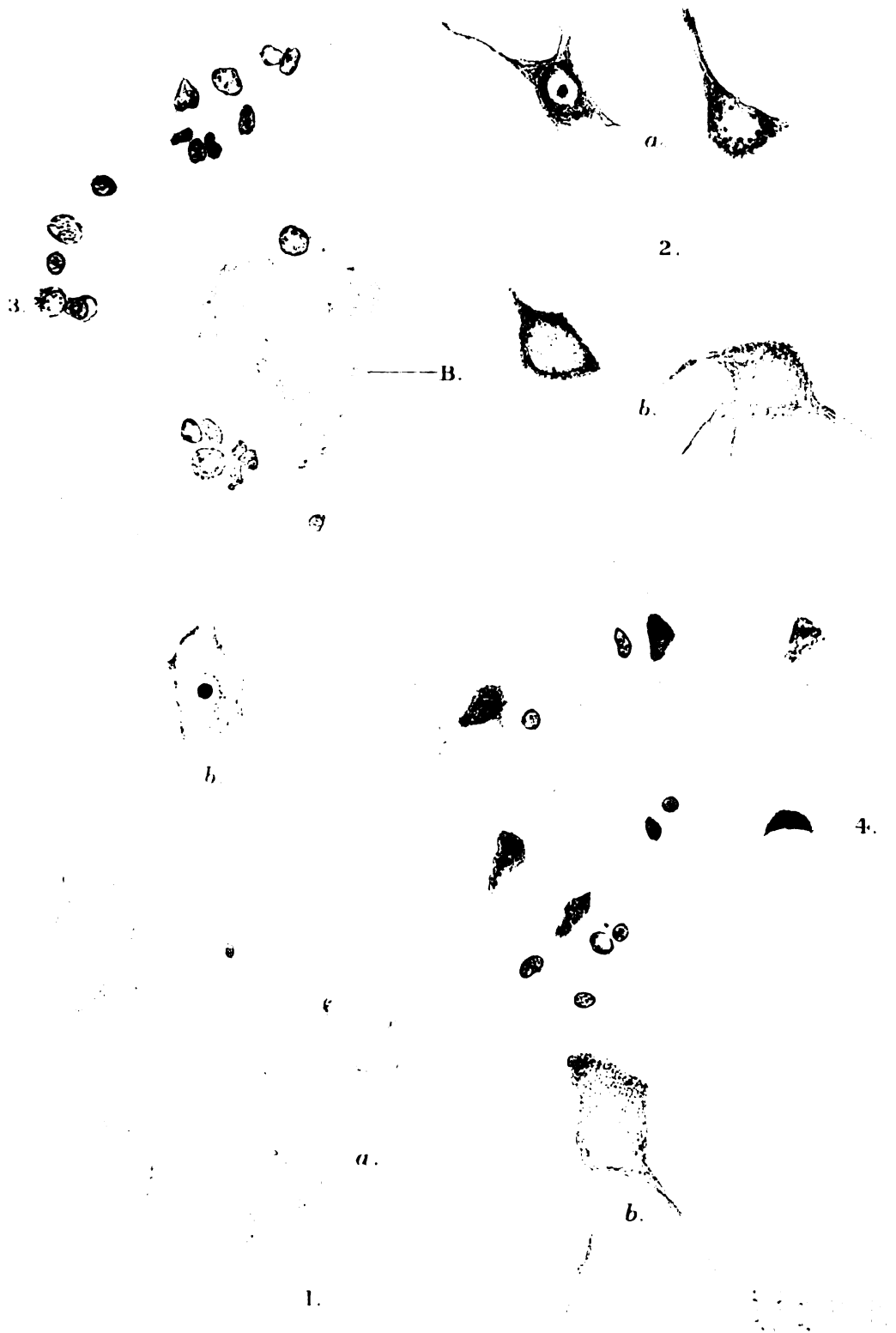
FIG. 1.—(a) Pigmented and atrophic degenerated Betz cells from the top of the ascending frontal convolution; (b) large Betz cells showing a less advanced degeneration.

FIG. 2.—Anterior horn cells showing two cells (a) with fairly normal Nissl pattern, and (b) two cells with pigmentary degeneration: in the one in which this is most advanced the processes of the dendrons are absent. Magnification 250. Nissl polychrome staining.

DEMENTIA PRÆCOX.

FIG. 3.—Section of the top of the ascending frontal convolution showing a large Betz cell B stained pink; there is no appearance of a Nissl pattern: the nucleus is not seen owing to its eccentric position. In the neighbourhood there are several groups of blue stained proliferated neuroglia nuclei.

FIG. 4.—The same section showing the smaller and medium sized pyramidal cells in which there is less evidence of morbid change than in the cells of the deeper layers. Moreover there is less evidence of neuroglia nuclear proliferation. Magnification 500. Polychrome eosin stain.



PRELIMINARY NOTE ON THE MICROSCOPIC
INVESTIGATION OF THE BRAIN IN CASES
OF DEMENTIA PRÆCOX.

BY F. W. MOTT, M.D., F.R.S.

THE microscopic investigation of this case is of interest for comparison with other cases of longer duration, in which the dementia is more pronounced. It was the first case which Dr. Koch used for his chemical observations.

G. S. Admitted to Claybury, January 29, 1904. Aged 24, single. Occupation a chairmaker, earning 18s. a week. He was a total abstainer, and as a lad, very bright and intelligent. He was in the seventh standard in the Board School. He was always a very delicate lad and was depressed for years before he came to the Asylum. He told his brother that he knew his mind was becoming affected, and the knowledge of his condition, together with the fact that he was aware that his sister had become insane at the age of 21, made him much worse.

His sister was formerly at Claybury but was transferred to Leavesden. His breath used to smell very bad and he worried about this. He would talk to imaginary persons and spit at the wall.

Family History.—Mother is delicate and of a nervous temperament, the father died of typhoid fever ten months ago. The mother's uncle was insane. No phthisis or intemperance in family. Sister, aged 33. Sister, aged 31, at Leavesden Asylum. When she visited her brother the A.M.O. considered her insane. She is apprehensive, restless, and deluded, according to the report of the Medical Superintendent. Brother, aged 30, married, who gave me the information; he has a pale, emotionless face, but talks quite rationally; he has four children all healthy. Sister, aged 28. Sister, aged 26. Six in all, the patient is the youngest.

Condition of Patient on Admission.—Physical examination. Heart sounds normal. Lungs, breathing vesicular. Pupils react to light and accommodation. Knee-jerks present. Plantar reflexes not obtained.

Mental State.—He is weak minded, dull and listless, and states that he has had worries and troubles for months, with headache. He is reserved and indifferent to his surroundings; hears voices

talking to him but thinks they may be due to his imagination. He sits about in a self contained passive attitude with his head bent on his chest and an absurd expression. He can be roused from this state and made to attend for a short time, but soon relapses into his former state as if he were unable from brain fatigue to continue the effort of attention. Diagnosis: dementia præcox. He later developed signs of phthisis and died March, 1905. A few days before he died his brother saw him and he told me (F.W.M.) that he talked sensibly to him, and ate some grapes and bananas which he took him. He was, however, indifferent to his brother leaving him and expressed no wish to accompany him.

Abstract of Post-Mortem Notes.—*Post-mortem* six hours after death, body in cold chamber. Body emaciated. General appearance imbecile. Small amount of downy hair on his face. Eyes set too close together. Ears rather large and simply formed. Teeth good. Palate very high and narrow. Dura mater natural. Sub-dural space, some excess of fluid. Pia-arachnoid, very slight local thickening and opacity, strips rather more readily than natural. Sub-arachnoid space, no excess of fluid. Encephalon, weight 1,365 grms, œdematous. Right hemisphere, 585 grms. Left hemisphere, 590 grms., 568 grms. stripped. Cerebellum, pons and medulla, 175 grms.

Description of Left Hemisphere stripped.—The hemispheres are of good size, but the convolutional pattern is not complex and the gyri generally are large. The sylvian angle is somewhat acute. There is a very deep and long parallel fissure which runs into the whole extent of the inferior parietal lobule. The fissure of Rolando has a deep bay in its second quarter. The pars basilaris and pars triangularis of Broca are well developed. There is a very deep and distinct pre-central, the superior and inferior portions of this furrow being joined. The post-central is much broken up by annectants. The pars horizontalis and pars occipitalis of the intraparietal are very distinct, the latter joins the lateral occipital, the two forming a very distinct lunate shaped sulcus. The external parietal occipital is rather unusually large and deep. The insula is simply convoluted especially in its pre-central portion. There are three very distinct transverse gyri of Heschl. On the mesial aspect the pattern is very simple, and there is a tendency towards the appearance of an orbital keel. The parts of the calloso marginal fissure are distinct. There is a very marked rhinal fissure almost joining the collateral. The latter is very long and deep. There is a long straight sub-calcarine and a very deep internal parietal occipital. The extremity of the calcarine extends just round the occipital pole. Little or no obvious wasting. Ventricles, not dilated, no granularity. Fourth ventricle, a few very fine granulations in lateral sacs only.

Cause of Death.—Tuberculosis of lungs.

Other Pathological Conditions.—Tuberculosis of liver, spleen and kidneys. Tuberculous ulceration of small intestine.

Microscopic Examination of the Brain, by modified Nissl method and by the neurofibril method of Cajal. Various regions were examined, but the most interesting and reliable observations were made from sections of the top of the ascending frontal where the giant Betz cells are situated. In all regions it appeared to me that there was a deficiency in number of the pyramidal cells of the cortex when compared with the normal. The supra-granular layer of pyramids are relatively to the infra-granular layers better stained. There is no vascular congestion. The deeper layers of Meynert are faintly stained, and the Betz cells show a marked deficiency of chromophilous substance, the nucleus is swollen and clear, pale, irregular in outline and often eccentric. The cytoplasm appears as if hydration had occurred, the edges of the cell are ragged and crumbling. In the deeper layers especially, but throughout the cortex and subjacent white nuclei there is a marked nuclear proliferation. Examined with a high power, a section stained with polychrome and eosin shows that these proliferated nuclei are the nuclei of young actively dividing neuroglia cells (*vide* fig. 4, plate iii.) In some groups six to eighteen cells are seen, affording obvious signs of this active proliferation. There are relatively only a few older glia cells with pink stained protoplasm and star-like processes. But these are to be found, likewise all stages between a nucleus with a thin rim of pink stained protoplasm to a well developed astrocyte. These are not found in the most superficial layers as in general paralysis and alcoholic dementia.

Sections stained by Cajal's neurofibril method showed that the pyramidal cells possess neurofibrils like a normal cell; in fact very beautiful specimens were prepared showing the neurofibrils in all the pyramidal layers. They did not show so well in the large Betz cells.

Whether these changes in the large Betz cells can be associated with the katatonic condition, and whether this deficiency of stainable (nucleo-proteid ?) substance in the deeper layers of cells can be in any way correlated with Dr. Koch's chemical observations, it is impossible to say.

The duration of the case is short compared to most cases of dementia præcox; the other cases examined by Dr. Koch were of much longer duration. It is of interest to observe that the pyramidal layers of cells, although apparently deficient in number, showed less change than the deeper layers and this fact may possibly be correlated with the statement of the brother, that a few days before his death he had talked sensibly to him. In four

other cases in which there was well marked dementia, mental symptoms had existed three and a half years, five years, nine years and thirteen years respectively.

In all of these cases there were well marked evidences of degenerative changes in the pyramidal cells and in two cases a diminution and attenuation of the myelin sheaths of the cortical fibres. For comparison, however, with G.S. we will take F. L. M. O., admitted to Claybury, May, 1903, aged 24, died September, 1906. Mother nervous, father epileptic. The patient was intelligent and reached the seventh standard in school. Before she was affected mentally was able to earn 27s. a week. State on admission: Depressed, melancholy and had lost her memory, stuporose at times and the subject of auditory hallucinations and delusions. I saw her in 1905 on several occasions. She sat in a chair emotionless and indifferent to her surroundings; instead of answering questions put to her, she would repeat, parrot-like, the phrase. There was slow automatic obedience to command and a tendency to assume fixed attitudes. Her face was immobile and emotionless, the hands cold, clammy and expressionless. She would remain for a time in any attitude she was placed. She would repeat automatically and in a monotone, abusive and obscene language she heard other patients utter without displaying any emotion or restless action. At times, however, and without any apparent cause, she would suddenly become impulsive and destructive, giving the attendants considerable trouble.

She died September, 1906, of tuberculosis of lungs and intestines. Microscopical examination of the brain by Dr. Stewart showed diminished depth of cortex; all the layers are less than normal in depth and the number of cells in each layer diminished. The layer of small pyramids was apparently less affected than the medium and large sized pyramids, but all showed marked chromolytic changes and an eccentric nucleus was evident in some of the large pyramids. The fibrils by Cajal's method appeared broken up and certainly did not exhibit the same normal appearance presented by the pyramidal cells of the previous case. There was an active proliferation of glia cells, generally seen in clusters around the defective ganglion cells.

A further communication on this subject by Dr. Stewart will appear later.

SOME CHEMICAL OBSERVATIONS ON THE NERVOUS SYSTEM IN CERTAIN FORMS OF INSANITY.

(*Preliminary Paper.*)

BY WALDEMAR KOCH.

*Assistant Professor of Biological Chemistry, University of Chicago;
From the Pathological Laboratory of the London County Asylums.*

AFTER spending some time in devising reliable methods for the chemical study of the nervous system, the application of these methods to certain forms of insanity was suggested to me by Dr. F. W. Mott, on account of the possibility of throwing new light on the pathology of these diseases. The primary dementia of adolescence or dementia præcox was suggested by him as perhaps the best type of insanity, in view of the fact that neither the macroscopic nor the microscopic evidence could in any way account for the symptoms. In the course of the work a number of observations of general interest to this subject were collected, which are here put together.

In devising these methods for the complete quantitative analysis of nerve tissues, my attention was early directed to the possible existence of compounds not proteids which should contain sulphur. There are to be found in the literature occasional references to such a possibility. Thus, Kossel¹ mentions the presence of sulphur in his preparation of protagon, and Thudichum² describes a similar mixture, which he calls a "sulphatid," on account of its sulphur content.

As cerebrin can be isolated from the mixture called protagon, I first tested a preparation of cerebrin, which, at

¹ Kossel. *Zeitschrift für Physiologische Chemie*. 1893, xvii., 436.

² Thudichum. "Die Chemische Konstitution des Gehirns des Menschen und der Tiere." 1901. F. Piezcker, Turbingen.

that time, was supposed to be reasonably pure, and was surprised to find as much as 0·8 per cent. sulphur. The further purification was continued, and after the sulphur had been reduced to 0·07 per cent. by several recrystallisations from glacial acetic acid and alcohol, the conclusion that cerebrin does not contain sulphur as an integral part of its molecule seemed justified. In this purification the mother liquors were, however, saved with a view to isolating the sulphur compound.

By precipitating the glacial acetic acid mother liquors with alcohol, alternately extracting with cold ether and recrystallising from alcohol, controlling the manipulations by frequent determinations of sulphur, a substance was finally obtained, which contained 1·3 per cent. S. and 0·6 per cent. P., and was mixed, or combined with about 43 per cent. of cerebrin (determined by the amount of galactose split off with 1 per cent. hydrochloric acid). This compound or mixture contained no loosely combined sulphur as determined by testing with lead acetate and sodium hydrate. On standing over night in water, or on boiling with acid, an appreciable amount of sulphates could be detected in the filtrate.

During the process of purification of the above compound a sticky mass remained behind, insoluble in hot alcohol and glacial acetic acid, but soluble in chloroform, from which it could be precipitated by alcohol. This substance contained no cerebrin, but almost 60 per cent. of kephalin (determined by the methyl groups) and 2·1 per cent. sulphur.

It is evident from these preliminary results that a sulphur compound exists, which contains most of its sulphur in an oxidised form, and has a tendency to either combine with or to adhere very firmly, mechanically, to the lipoids (cerebrin, kephalin, and also lecithin). As any attempt to split off this compound from this combination was almost sure to lead to its destruction, a search was begun to discover it, if possible, in an uncombined form.

By extracting nerve tissues with dilute alcohol and purifying the filtrate by a method to be described in detail

later, a compound was finally obtained, free from cerebrin and kephalin, which contained, sulphur 3·6 per cent., phosphorus 1·9 per cent. This compound contained no loosely combined or cystin sulphur, but split off sulphates readily on standing in alkaline solution. At present the relation of this compound to the one combined with cerebrin, on the one hand, and kephalin on the other hand, has not been determined. Sulphur seems to occur in all of them in a form capable of splitting off readily as sulphate. There is also a constant relation of the sulphur to phosphorus (2 in 1) which points to the presence of phosphorus in the molecule.

As the yields of this sulphur compound are very poor, an attempt was made to find it in some other tissues besides the nervous system. The following table gives the results expressed in parts per thousand as inorganic sulphur, *sulphates*, extractive sulphur, *partially represented by sulphur compound in uncombined form*, and sulphur combined with lipoids.

TABLE I.

Moist tissue	Inorganic sulphur, sulphate	Extractive sulphur, uncombined compound, probably no albumose	Lipoid sulphur, combined with cerebrin, kephalin	Total sulphur
Submaxillary gland ..	0·033	0·064	0·048	0·145
Testicle	0·026	0·124	0·059	0·209
Liver	0·047	0·321	0·096	0·464
Voluntary muscle ..	0·082	0·350	0·020	0·452
Spinal cord	0·156	0·205	0·668	1·029

The above table makes it quite evident that sulphur must play an important part in the nervous system. Not only is the total fully twice as great, but the lipoid sulphur, such as would be represented by the cerebrin sulphur and kephalin sulphur compounds described in the beginning, is from six to thirty times as great as that in the other tissues. The extractive and inorganic sulphur are practically as high as in any of the other tissues. Analyses of the grey and white matter separately indicate that these sulphur compounds may be pretty generally distributed in different parts of the nervous system, and are probably not confined to the medullated fibres alone, although present there

in somewhat larger amount, especially in the combined or lipid form.

If, as the above results indicate, there is in the nervous system a metabolism which leads to a compound from which sulphur can be readily split off as sulphate, it seems of interest to examine the cerebro-spinal fluid for sulphates, especially as very little attention has been given to this point.^{1 & 2} A number of factors seem to influence the results.

TABLE II.

	Page Claybury p.-m. Sex	Time after death. Hours	Phos- phorus. Parts per million	Sulphur. Parts per million	Proteids. Per cent.	Reducing sugar
During life	J. A.	During life	—	Trace*	—	—
	M. B.	" "	24	"	0.036	Positive.
	"	" "	26	"	—	"
	C. B.	" "	21	"	—	"
Direct to post-mortem	107, F., '05 ..	2 h.	49	12	0.077	Present.
	49, M., '05 ₂ ..	2 h.	55	39	—	—
	46, M., '05 ₂ ..	2 h.	59	14	—	—
	50, M., '05 ₂ ..	2 h.	35	8	—	—
	58, M., '05 ₂ ..	4 h.	—	7	0.090	—
	66, M., '05 ₂ ..	7 h.	85	14	0.043	Present.
	67, M., '05 ₂ ..	8 h.	65	5	0.047	"
	47, M., '05 ₂ ..	9 h.	—	9	—	—
	56, M., '05 ₂ ..	10 h.	74	62	—	—
Kept in cold chamber	101, F., '05 ..	11 h.	191	13	0.10	Negative.
	89, F., '05 ..	12 h.	110	10	—	—
	96, F., '05 ..	14 h.	200	29	—	—
	57, M., '05 ₂ ..	14 h.	—	54	—	—
	65, M., '05 ₂ ..	16 h.	180	67	0.14	Present.
	104, F., '05 ..	18 h.	110	16	0.06	Negative.
	55, M., '05 ₂ ..	20 h.	74	12	—	—
	105, F., '05 ..	24 h.	71	62	0.06	Negative.
	53, M., '05 ₂ ..	25 h.	124	17	—	—
	69, M., '05 ₂ ..	28 h.	60	15	0.07	Present.
	48, M., '05 ₂ ..	41 h.	105	19	—	—
	99, F., '05 ..	48 h.	190	14	0.10	Present.
	59, M., '05 ₂ ..	60 h.	325	63	—	—

* 10 cc. yield about 0.1 mg. B_2SO_4 .

It is very difficult, therefore, to draw any conclusions from only twenty-five determinations so far made, and the following analysis of the results is merely given to indicate the

¹ Nauratzki, *Zeitschrift für Physiologische Chemie*, 23, 532.

² Pauzer, *Weiner Klinische Wochenschrift*, 1899, 805.

direction in which further investigation may proceed. The full description of the method for making the proteid, sulphate and phosphate estimations is given in the experimental part of the paper.

The first factor of importance to consider is the influence of *post-mortem* change. The following table gives the results arranged according to the time of the *post-mortem* examination.

The phosphorus values increase consistently, while the sulphur shows extreme variations. The following table of averages serves to make this point a little clearer.

TABLE III.

POST-MORTEM CHANGES (AVERAGES).

	Phosphorus	Sulphur	Proteid	Remarks
During life	24	trace	0·036	Average of 4 analyses.
Direct to P.M. 2-10 hours	61	20	0·064	" " 9 "
Kept in cold chamber } p.m. 10-48 hours	130	26	0·090	" " 12 "
Kept in cold chamber } p.m. 60 hours	325	63		One analysis.

The last case in which cerebro-spinal fluid was taken sixty hours after death, evidently shows the result of considerable *post-mortem* change, especially in the phosphorus, and will not be further considered. Comparing the other cases, a gradual and consistent increase of the phosphorus and proteid is to be observed, while the sulphur average shows a sudden increase immediately after death, and then remains fairly constant. The extreme variations in the sulphur cannot, therefore, be accounted for by a later *post-mortem* change, and other factors must be considered. Among these is the age of the patient, as will be evident from the following table.

As the *post-mortem* variations just about eliminate one another in this table the phosphorus average is nearly constant, while the sulphur is more than doubled in old age, indicating a greater instability of the sulphur compound. The individual variations are, however, great enough to suggest that still other factors must be concerned.

TABLE IV.

Page.	Claybury, p. m.	Sex	Age Years	Phosphorus Parts per million	Sulphur Parts per million
53, M., '05 ₂	..	..	74	124	17
57, M., '05 ₂	..	..	72	—	54
105, F., '05	..	..	68	71	62
48, M., '05 ₂	..	..	67	105	19
56, M., '05 ₂	..	..	66	74	62
49, M., '05 ₂	..	..	62	55	39
46, M., '05 ₂	..	..	55	59	14
Average ..			..	81 ..	.. 38
99, F., '05	..	..	45	190	14
55, M., '05 ₂	..	..	41	74	12
107, F., '05	..	..	41	49	12
50, M., '05 ₂	..	..	41	35	8
58, M., '05 ₂	..	..	39	—	7
67, M., '05 ₂	..	..	39	65	5
66, M., '05 ₂	..	..	38	85	14
104, F., '05	..	..	35	110	16
89, F., '05	..	..	27	110	10
69, M., '05 ₂	..	..	24	60	15
96, F., '05	..	..	15	200	29
Average ..			..	98 ..	.. 13

In Table V. the cases are grouped as much as possible according to the nature of the illness. The mental condition is also given.

It would be manifestly unsafe to draw any conclusions from the above table with regard to clinical condition without further confirmation. It is interesting to note, however, that all the really high results occur in the old subjects, although there are a number of old cases which come low. The highest result, 66·7, is given by a case of chronic mania, which could not be called very old. Another case of recurrent mania, however, gives a fairly low result. The cases of general paralysis of the insane all give unusually low results. This may be due to the fact that they are, as a rule, fairly young, and that the great excess of fluid to be found in these cases dilutes the sulphates. There is no lack of the sulphur compound in the nervous system, as analyses by Mr. Goodson on three cases of general paralysis indicate. Before any conclusion can be reached it will be necessary to compare with the above a series of analyses of cerebro-spinal fluid from normal individuals.

TABLE V.

Page Claybury, p.-m. Sex	Age	Phosphorus. Parts per million	Sulphur. Parts per million	Cause of death	Mental state
89, F., '05	27	110	10	Tuberculosis ..	Chronic melancholia ; little dementia.
66, M., '05 ₂	38	85	14	„ ..	General paralysis of insane.
55, M., '05 ₂	41	74	12	„ ..	Acute melancholia ; no dementia.
99, F., '05	45	190	14	„ ..	Chronic melancholia with dementia.
46, M., '05 ₂	55	59	14	Acute tuberculosis	Alcoholic dementia, two years standing.
105, F., '05	68	71	62	Chronic Bright's disease	Melancholia ; senile dementia.
57, M., '05 ₂	72	—	54	Chronic Bright's disease	Senile melancholia with dementia.
50, M., '05 ₂	41	35	8	Epithelioma of scrotum	General paralysis of insane.
53, M., '05 ₂	74	124	12	Carcinoma of pleura	Senile dementia.
69, M., '05 ₂	24	60	15	Acute dysentery..	Recurrent mania.
104, F., '05 ₂	35	110	16	„ „ ..	Alcoholic dementia.
67, M., '05 ₂	39	65	5	Hypostatic pneu- monia and general paralysis	General paralysis of insane.
58, M., '05 ₂	39	—	7	Lobar pneumonia	General paralysis of insane.
107, F., '05	41	49	12	Broncho-pneumo- nia	General paralysis of insane.
47, M., '05 ₂	53	—	9	Broncho-pneumo- nia	General paralysis of insane.
43, M., '05 ₂	67	105	19	Gangrenous pneu- monia	Alcoholic dementia.
49, M., '05 ₂	62	55	39	Gangrenous pneu- monia	Melancholia ; second- ary dementia.
96, F., '05	15	200	29	Septicæmia ; sup- purative nephri- tis	Epileptic imbecile.
56, M., '05 ₂	66	74	62	Septicæmia ; sup- purative nephri- tis	Chronic melancholia ; secondary demen- tia.
65, M., '05 ₂	51	180	67	Acute appendici- tis ; peritonitis	Chronic mania.

It would appear, then, from these analyses that sulphates are absent from the cerebro-spinal fluid during life, which accounts for the fact that they have hardly received any mention so far. Two reasons may be assigned for this absence ; either sulphates are not formed during life, or more probably they are carried away by the blood. After

death, the circulation having ceased, they now diffuse into the cerebro-spinal fluid. It might be suggested that the blood is the source of these sulphates, but several analyses made on blood and blood serum, collected from the vena cava, indicate that this possibility need not be considered. As these sulphates must come, therefore, from the tissues of the nervous system it is evident that they are derived from the sulphur compounds which, as mentioned above, are capable of splitting off sulphates.

Two factors would, therefore, come in to determine the amount of sulphates in the fluid, first the amount of sulphur compound in the tissues, and secondly the relative ease with which the sulphate can be split off. The first point can be determined by a chemical examination of the tissues. The increase in sulphates after death takes place so quickly that one is almost tempted to correlate this change with the cessation of physiological activity and cell death. Thus, in one case—49 male—enough sulphates are split off in two hours after death to bring the concentration calculated in per cent. of sulphuric acid up to 0.012 per cent. The development of an acid reaction in nerve tissues after death has usually been assigned to the formation of lactic acid, merely on account of the analogy with muscular tissue. This lactic acid is supposed to be derived largely from sugar, possibly also from any alanin that may be present in the proteid molecule. With regard to the latter source we know nothing of the quantities available, and as hydrolysis must precede the change it could hardly go on with sufficient rapidity to be a factor, especially as autolysis does not start until an acid reaction is established. With regard to the sugar, the change also cannot be very rapid, as I have occasionally found sugar in the cerebro-spinal fluid, as much as twenty-four and forty-eight hours after death (see Table II.).

The sulphates, on the other hand, reach their maximum very quickly and then change very little. It is true that lactic, acetic, and even formic acids have been isolated from nerve tissues, but nothing is known of their relative amounts, and besides, the state of preservation of the

tissues, from which they were isolated, was not above suspicion.

The results obtained from the examination of cerebro-spinal fluids, although not sufficient to lead to any definite conclusions, especially with regard to the correlation of clinical observations and analytical results, nevertheless point very strongly to the importance of a sulphur metabolism, and are thus in harmony with the facts already cited. The continuation of these analyses is sure to lead to interesting results.

In harmony with the observations so far recorded are the results of the chemical analysis of the brains of five cases of primary dementia, which also point to the importance of sulphur to the nervous system. The cases were selected and placed at my disposal for chemical examination by Dr. F. W. Mott. As a control on the analytical technique, the analysis of the brain of a case with no mental symptoms was also made. Brief notes of the cases are as follows: the hospital case coming first. The numbers of the cases are in continuation of cases previously reported.¹

Case 7.—K. R., London, Charing Cross Hospital, F., 06. Age 48.

Autopsy thirty hours after death. *Weight of brain*, 1,305 grammes. No wasting. Convolutional pattern simple. Nerve cells of cortex slightly oedematous, but otherwise normal.

Cause of death.—Gangrene of small intestine following operation for strangulated umbilical hernia.

Mental state.—Normal.

Case 8.—G. S., Claybury Asylum, 148, M., 05. Age 24.

Autopsy five hours after death. *Weight of brain*, 1,365 grammes. Some wasting. Slight excess of fluid. The Betz cells of the motor cortex show some chromolytic change. There are evidences of beginning neuroglia changes.

Cause of death.—Pulmonary tuberculosis.

Previous occupation.—Chairmaker's assistant. One year in asylum.

Diagnosis of mental state.—Primary dementia of adolescence.

Case 9.—C. H., Claybury Asylum, 36, M., 05₂. Age 35.

Autopsy ten hours after death (body kept in cold chamber).

¹ Koch and Goodson. *American Journal of Physiology*. 1904. xv. 272.

Weight of brain, 1,230 grammes. Considerable wasting. Large excess of fluid.

Cause of death.—Pulmonary tuberculosis.

Previous occupation.—Printer. Ten years in asylum.

Diagnosis of mental state.—Primary dementia.

TABLE VI.

GREY MATTER.

Constituents calculated in per cent. of dry tissue.

	NORMAL	PRIMARY DEMENTIA WITH TUBERCULOSIS				
	7 K.R.	8 G.S.	9 C.H.	10 M.A.H.	11 C.E.N.	12 F.L.M.O.
Simple proteid ..	29.4	33.4	31.6	29.7	29.4	30.1
Nucleo proteid ..	16.3	18.2	19.0	20.4	20.8	19.9
Lecithins and kephalins)	24.5	23.2	22.5	22.3	21.5	22.5
Lipoid sulphur compounds)	1.4	0.3	0.4	1.3	0.7	0.8
Cerebrins	7.9*	8.9	10.5	—	—	—
Extractives	8.4	7.6	9.0	—	—	—
Ash	4.8	5.5	5.9	—	—	—

TABLE VII.

WHITE MATTER.

Constituents calculated in per cent. of dry tissue.

	NORMAL	PRIMARY DEMENTIA WITH TUBERCULOSIS				
	7 K.R.	8 G.S.	9 C.H.	10 M.A.H.	11 C.E.N.	12 F.L.M.O.
Simple proteid ..	14.5	11.5	13.1	13.2	12.6	12.3
Nucleo proteid ..	14.2	16.6	15.7	15.1	15.2	15.1
Lecithins and kephalins)	27.9	26.5	26.6	26.5	22.4	25.3
Lipoid sulphur compounds)	4.7	3.5	—†	4.6	5.2	5.4
Cerebrins	17.7*	16.8	16.8	—	—	—
Extractives	4.0	3.1	3.5	—	—	—
Ash	2.1	2.4	2.3	—	—	—

* These figures were taken from analyses by Mr. H. Goodson.

† Estimation lost.

The difference between the totals of these analyses and 100 approximately represents the amount of cholesterin, which was not estimated.

Case 10.—M. A. H., Claybury Asylum, 149, F., 06. Age 27.

Autopsy sixty hours after death (body kept in cold chamber).

Weight of brain, 1,250 grammes. Very little wasting. No excess of fluid.

Cause of death.—Advanced pulmonary and intestinal tuberculosis.

Previous occupation.—Leather stitcher. Five years in asylum.

Diagnosis of mental state.—Primary dementia.

Case 11.—C. E. N., Claybury Asylum, 131, M., 06. Age 35.

Autopsy fifty-one hours after death (body kept in cold chamber). *Weight of brain*, 1,325 grammes. Some wasting. Slight excess of fluid. Microscopic examination not made.

Cause of death.—Pulmonary tuberculosis and gangrene of lungs.

Previous occupation.—Surveyor. Four years in asylum.

Diagnosis of mental state.—Primary dementia.

Case 12.—F. L. M. O., Claybury Asylum, 8, F., 06₂. Age 27.

Autopsy eight hours after death. *Weight of brain*, 1,190 grammes. Very little wasting. Some excess of fluid. Microscopic examination not made.

Cause of death.—Pulmonary tuberculosis.

Previous occupation.—Passed VIIth. Standard in school. Taught music. Three years in asylum.

Diagnosis of mental state.—Primary dementia.

The methods of chemical analysis were those of Koch, and Koch and Goodson. The grey matter in each case was taken from the frontal and motor cortex, the white matter from the corpus callosum.

Grey matter.—The most apparent result in the accompanying table is the great decrease of lipoid sulphur in the cortical grey matter. This is of interest when we consider that this form of sulphur is especially characteristic of the nervous system (*cf.* Table I.). Whether this change is due to the effects of the tuberculosis toxin alone or whether the conditions leading to the dementia of adolescence also play a rôle can only be decided by the collection of more data. Case 10 does not show the change so marked as the others. There is, however, in Case 10 as well as in the other analyses, a decrease in the water soluble sulphur (*cf.* Experimental Part) with an increase of the inorganic sulphates. Besides these marked changes there is a perceptible decrease of the lecithins and kephalins. The larger amount of nucleins as compared with the normal is not of much significance as the normal is an unusually low result. Case 8 is higher in simple proteid, a change which can be usually associated with changes in the neuroglia tissues.

White matter.—The results obtained for the corpus callosum show less variation from the normal than the cortical grey matter, only in one case is the lipoid sulphur appreciably diminished.

These analyses are to be regarded only as preliminary and merely indicating the direction in which the work will be continued.

It appears, therefore, from the facts cited above, that the nervous system, or some part of it, in the course of its metabolic activity, forms a compound or compounds which are capable of splitting off sulphates, and furthermore, have a strong tendency to combine with the lipoids. The source of this sulphur must be the proteid, which is the only form in which unoxysidised sulphur enters the system under normal conditions, and the change consists in an oxidation.

We obtain, therefore, for the first time, a suggestion as to the use the nervous system makes of the large excess of oxygen with which it is so well supplied, and of which it seems to be in such constant need. The water soluble or extractive form of sulphur compound isolated, judging from its low percentage of sulphur, must have a fairly high molecular weight, it gives, however, no longer any of the proteid or even peptone reactions (biuret, precipitate with phospho-tungstic acid, &c.), but behaves rather like the polypeptids, in that it reacts with naphthylisocyanate. As this reaction has to be carried on in an alkaline solution, however, the percentage of sulphur in the product decreases rather than increases. Whatever the relation of this compound, or the metabolic change by which it is formed, has to mental activity or to different forms of insanity must be left to further study. The chemical study of the structure of this compound is also sure to give some insight into the mechanism of its formation.

EXPERIMENTAL PART.

1.—*Preparation of the Sulphur Compound (Water Soluble or Extractive Form).*

Heat the nerve tissue with an equal weight of 90 per cent. alcohol for several hours; allow to cool and filter. Make filtrate acid with sulphuric acid, and add an excess of phospho-tungstic acid; allow to settle and filter. To the filtrate add a slight excess of barium hydrate, filter as soon as possible, and make acid with oxalic acid. Evaporate in stream of dry air to small bulk, filter; test with phospho-

tungstic acid, and repeat purification if necessary. To prepare the free compound in an impure state, dissolve in glacial acetic acid and precipitate with alcohol.

Such a preparation gave, on analysis :

	I.	II.	III.	
Sulphur ..	3.6	3.75	†3.0	†Contained considerable admixture of barium acetate.
Phosphorus ..	1.9	—	1.2	
Nitrogen ..	6.0?	—	—	

To purify, shake a solution of this compound (or the filtrate obtained above before precipitation with alcohol) with naphthylisocyanate in slightly alkaline solution. Filter : make filtrate acid with hydrochloric acid. The naphthylisocyanate compound separates out and gives on analysis—

Phosphorus	0.89.
Sulphur	1.93.

A nitrogen determination was not made, as the presence of the isocyanate would introduce an error, the extent of which could not be determined. The compound must, however, have contained nitrogen to react with the isocyanate.

The substance obtained in the free state, as given above, has the following properties :—Soluble in water and glacial acetic acid. Insoluble in alcohol, ether and chloroform. Does not precipitate with phospho-tungstic acid solution, and gives no reaction with ferric chloride, similar to Siegfried's phosphocarnic acid. It is free from kreatin or kreatinin, and does not yield any lead sulphide with sodium hydrate and lead acetate. For comparison the solubilities of the lipoid sulphur combinations are given.

Cerebrin sulphur combination : Soluble in hot alcohol and glacial acetic acid ; insoluble in ether, chloroform and water.

Kephalin sulphur combination : Soluble in chloroform, insoluble in alcohol, ether and glacial acetic acid, even on heating.

The possible relations of these compounds to Bethe's Nissl acid and fibrillic acid, need hardly be discussed, as his compounds were not sufficiently well characterised for comparison of chemical properties or composition. His

Nissl acid may correspond somewhat to the soluble extractive form of my sulphur compound, and the fibrillic acid to the kephalin combination, although the method adopted by him for isolating fibrillic acid chemically would hardly lead to anything but impure kephalin. I have refrained from attempting to name the compound or compounds here described as their properties have not been sufficiently well determined to justify this.

II.—*Method of Analysing Cerebro-spinal Fluid for Proteid, Sulphates and Phosphates.*

Cerebro-spinal fluid collected by lumbar puncture, or from the lateral ventricles, is centrifugalised, filtered, and 10 cc. placed in a beaker; 3 cc. of saturated ammonium nitrate solution, and five drops of nitric acid added. The mixture heated on the water bath until complete coagulation has taken place (the filtrate remains clear on saturating with ammonium sulphate). The coagulated proteid is filtered through a perforated Gooch crucible, washed with 0.1 per cent. ammonium nitrate solution, and then with alcohol, dried at 100° C. and weighed.

The filtrate is taken before the washing with alcohol is begun, concentrated to 10-15 cc. and 2 cc. of 1 per cent. barium nitrate solution, added while boiling. The barium sulphate, after standing over night, is filtered off and weighed in the usual way. With the filtrate a phosphorous estimation is made by the molybdic method, with subsequent precipitation as magnesium ammonium phosphate in the usual way.

If more fluid is available, a test for reducing sugar is made with 1 cc. This method enables one to make a fairly complete analysis with only 10 cc. of cerebro-spinal fluid, which can easily be obtained by lumbar puncture under favourable conditions. Contamination with blood renders the estimation of little or no value.

In conclusion, it gives me great pleasure to thank Dr. F. W. Mott, F.R.S., for his many suggestions, and the Committee of the London County Council for their

liberality in placing at my disposal every facility for work. Dr. G. A. Watson greatly aided me in collecting material and looking up the clinical notes. The cerebro-spinal fluids collected during life were placed at my disposal by the kindness of Dr. G. F. Barham. The satisfactory analytical results obtained in the cases of primary dementia are largely due to the care taken in their collection and preliminary analysis by Mr. Sidney Mann. The investigation was made possible by a grant from the Rockefeller Institute for Medical Research.

CEREBRAL ANÆMIA IN RELATION TO LESIONS IN PSYCHOSES OF TOXIC ORIGIN.

BY F. W. MOTT, M.D., F.R.S.

*Physician to Charing Cross Hospital, Pathologist to the London County
Asylums and Director of the Pathological Laboratory.*

WHEN asked to undertake to act as Rapporteur for this subject at the Psychological Section of the International Medical Congress, I should have felt some diffidence in accepting the task had I not been informed that it was privileged to exercise wide discretion in the mode of treatment of this very difficult albeit very important subject.

Although it is a fact that in my experience, it is possible in very many cases of toxic psychosis to demonstrate changes of structure in the cerebral cortex, the exact relation these bear to the morbid mental phenomena exhibited during life cannot even be conjectured. Each new method of studying the normal histology of the central nervous system and the discoveries made thereby, have led not a few enthusiastic workers to predict a solution of the problems underlying mental action and even the still more difficult problem of diseases of the mind. Numbers of investigators working from many different standpoints have been and still are engaged in attacking this problem, but while there has been an abundance of histological detail and speculation regarding the correlation of histological changes with morbid mental states but little rests upon the solid basis of scientific requirement. When such an accurate and experienced observer as Nissl,¹ the inventor of the method which more than any other has been used with advantage for throwing light upon changes in structure of the nervous system, publicly states that we

¹ Neurol. Centralblatt, 1901, p. 483.

cannot be too sceptical in correlating cortical changes with mental diseases, and can only point to the probability of the plasma cells of Marscholko as a specific lesion of general paralysis, we may well hesitate in accepting any cortical changes as being evidence of specific toxic action.

Not until we can eliminate a number of other factors is it even safe to assert that the changes are directly caused by a toxin introduced from without or engendered within the body. First of all we have to eliminate *post-mortem* change; my observations, however, are not affected by this complication as the bodies are placed in a cold chamber very soon after death. Secondly, death in toxic psychoses is so frequently complicated by lung diseases of which tuberculosis is the most common, especially in subjects of dementia præcox, epileptic imbecility and melancholia. My experience indeed shows that the onset of the mental symptoms in dementia præcox and melancholia of adolescents so frequently coincides with the onset of tubercle that there must be a correlation indicating a depression of vital metabolism of the body generally and of the nervous system in particular, the latter being the result of an inherent defect of nervous potential.

It is impossible to say therefore whether the tubercular toxin is a cause or an additional factor in the production of the mental phenomena. Certainly a vicious circle tends to be produced; for refusal of food and impaired nutrition with slow and shallow respiration, and feeble circulation tend toward rapid progress of the infective process and an increased amount of the tuberculous toxin poured into the blood.

Certain changes have been found in the cortex in dementia præcox which will be related later on; they are probably not specific of this form of alienation; also they are probably not the result of tubercular toxin or the febrile state *per se*, but rather a result of a deranged metabolism of the cortical cells in which microbial toxins, auto-toxins, or cyto-toxins may be the predisposing or exciting cause. If the insane do not die from acute or chronic pulmonary tuberculosis, secondary or terminal microbial infections

occur in a great majority of the remainder of the cases from broncho-pneumonia, pneumonia, gangrene of the lung, dysentery, bed-sores, and cystitis, &c. Again chemical restraint by the continued use of narcotising agents in quelling convulsions and maniacal excitement may, as in the case of sulphonal, so alter the chemical composition of the blood as to depress the metabolism of the cortical cells and be responsible for histological changes. Moreover, in cases where there have been prolonged convulsions, *e.g.*, status epilepticus, and some cases of general paralysis, the mechanical conditions are such as to produce a vicious circle terminating in progressively increased venosity of the blood in the cortex, especially the portion supplied by the carotid arteries, and the veins of which drain into the longitudinal sinus. In fact, a pure case free from complications and intercurrent affections, *e.g.*, respiratory failure of considerable duration, asphyxia, cardiac failure, or some secondary microbial infection is rarely to be obtained. Thus cases of sudden death arising from injury, suicide, accident or some other cause, would be specially valuable for determining the relation of acute and chronic intoxications to lesions of the cerebral cortex. However, if a patient who has died of one of these various conditions has presented during life no delirium or mental confusion, and the cortical structures present no abnormality, whereas in another patient delirium, mental confusion, or even insanity occurred, and lesions of the cortical cells are found, we are justified in correlating the absence of mental symptoms in the former case to the absence of these changes and the existence of mental symptoms in the latter to the changes found *post mortem*. But we are not, therefore, justified in asserting that poisons introduced from without, microbial toxins or auto-toxins can produce specific lesions *per se*. The metabolic reactions of systems, groups, and communities of neurons to their environment may be altered by the toxic condition of the blood. An actual chemical combination may occur as in tetanus toxin, which has an elective affinity for the grey matter in the spinal reflex arc. Similarly other poisons may have an elective affinity for certain groups, or systems

of neurons with specific functions thus accounting for specific functional disturbances resulting from particular poisons. It is generally believed and widely taught that auto-toxins are the cause of many psychoses; but we are entirely ignorant of their source, the manner in which these poisons act *and of their chemical properties*.

The fundamental basis of the study of toxic psychoses in relation to cortical lesions is a knowledge of the chemistry of the normal neuron and the metabolism of the nervous system. By histo-chemical methods and elective stains it may be possible to differentiate the essential chemical substances of the neuron, to ascertain the changes which these substances undergo during functional activity and eventually to separate and prepare the substances for the determination of their exact chemical composition.

The most certain facts that we possess regarding the relation of chemical change to the functional activity of the cortex is the necessity of the oxygen supply by the arterial blood; and I shall give briefly the results of my histological examination of the cerebral cortex at various periods after ligation of the cerebral arteries in dogs, cats and monkeys. In dogs, it was found by Dr. Leonard Hill, who performed the experiments, that ligation of both carotids and both vertebral arteries produced only temporary functional defects. The animal on recovering from the anæsthetic exhibited in varying degrees, and as a rule for a few days, at most a week, symptoms pointing to loss of function of the cortical grey matter. The animal was in a condition like Goltz's dog with its cortex destroyed. It feebly wandered about with its legs splayed out, taking no notice of a flame, tobacco smoke blown in its nostrils or of its food, although when placed in its mouth it would eat it. A cat placed near did not excite attention, it would not answer to a call, sensory stimuli did not awaken in its cortex a psychical response. All these symptoms passed off more or less rapidly and no difference could be detected in its behaviour to that of a normal dog. Examination showed that collateral circulation had been restored by the anterior and posterior spinal arteries becoming as large as vertebrals.

DESCRIPTION OF PLATE I.

FIG. 1.—Cells from the crucial sulcus of a cat. Stained by Nissl. Magnification 375 diameters. *a*, Betz cells; *b*, small cells in the same layer; *c*, cells from the lowest portion of the pyramidal layer. *d*, cells from the upper part of the pyramidal layer.

FIG. 2.—Pyramidal cell with diffuse staining, from a cat after ligation of four cerebral arteries. Magnification 375 diameters. Stained by Nissl.

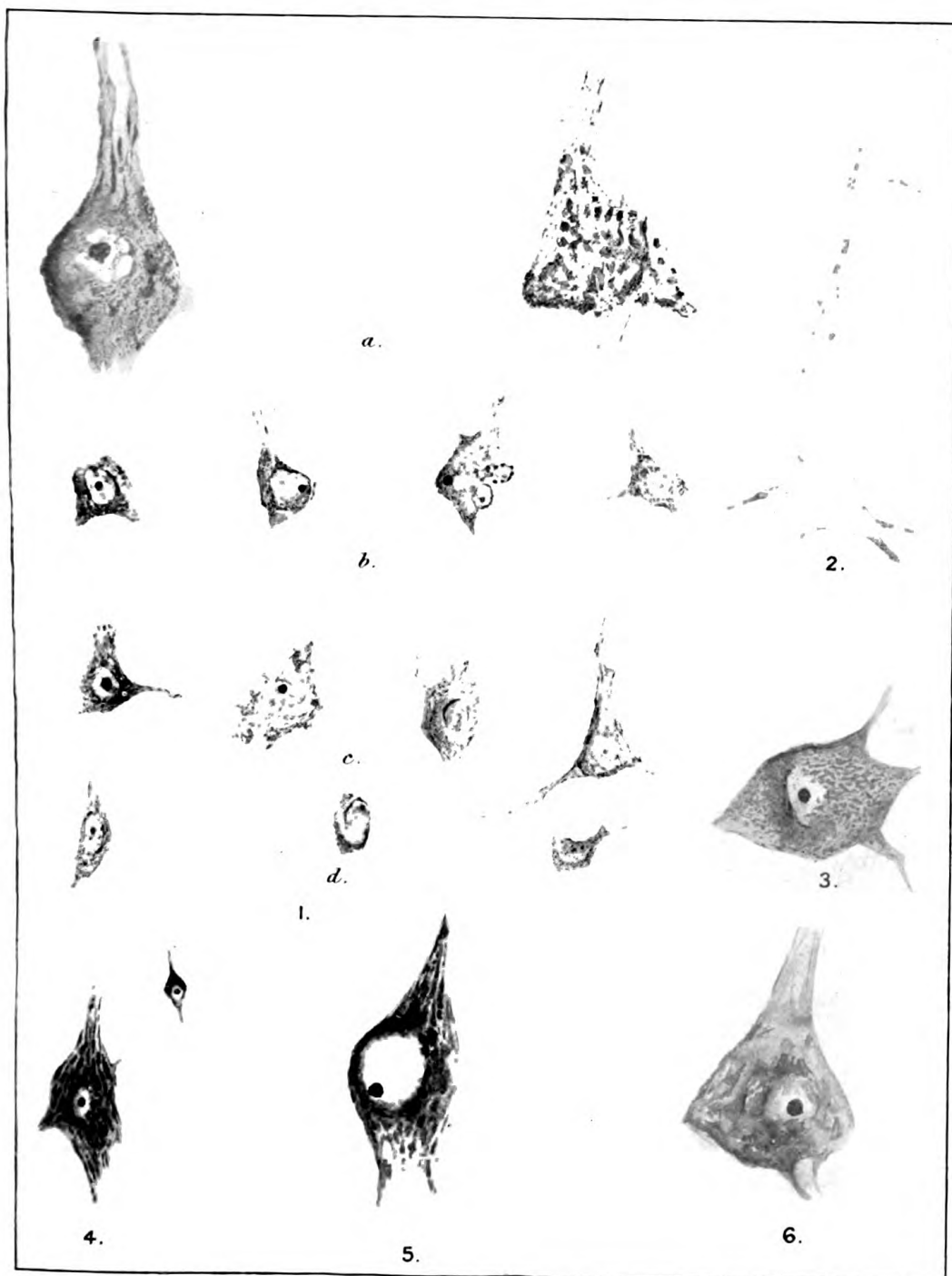
FIG. 3.—Pyramidal cell from a monkey five days after ligation of two carotids and one vertebral, showing swelling in the pyramidal cell, with diffuse homogeneous staining, owing to the stainable substance being scattered through the protoplasm of the cell as a fine dust. Stained by Nissl. Magnification 375 diameters.

FIG. 4.—Cells from the cortex of a cat that died under the influence of an anæsthetic prior to ligation of arteries. Normal appearance of the cortical pyramidal cells stained by the Nissl method. Magnification 375 diameters.

FIG. 5.—Pyramidal cell of a dog after ligation of two carotids, one vertebral and one sub-clavian. Great swelling of the nucleus, advanced chromatolysis most marked at the periphery of the cell. Nissl method. Magnification 375 diameters.

FIG. 6.—Pyramidal cell of a dog after ligation of arteries, showing extreme chromatolysis with commencing extrusion of the nucleus. Nissl method. Magnification 375 diameters.

PLATE I.



In some instances a more profound cortical anæmia was produced by ligation of two carotids, one vertebral and one subclavian at a point before the vertebral is given off, thus leaving practically only one superior intercostal to carry on the circulation. In such cases the anæmia was more profound and sometimes caused death within twenty-four hours by the insufficiency of circulation in the medulla and choroid plexus; in those cases which survived, the dementia of the animal was more profound and more persistent and the histological changes observed in the cortex came on sooner and were more pronounced. Cats and monkeys, as a rule, died within twenty-four hours after ligation of the four arteries. Death followed convulsions, preceded by coma. The histological changes observed in such cases of complete anæmia were quite different to those observed in severe but partial anæmia (*vide* Plate I., fig. 2). It was found that faradic excitation of the cerebral cortex of animals with severe but not absolutely complete anæmia was followed by the characteristic motor responses, but there was a tendency to spread, and, even with a moderate current, for epilepsy to occur.

The motor path was open from the cortex and capable of conducting stimuli and this accounts for the fact that no paresis followed ligation of four arteries provided that the animal recovered by restoration of collateral circulation. Examination of the motor cortex of the brain at varying periods after the operation showed by Nissl method swelling of all the cortical cells. The nucleus large, pale and clear sometimes occupying an eccentric position, the Nissl substance diminished and incrusting the fibrils in the form of threads but present in the large Betz cells in fair abundance (*vide* Plate I., figs. 1, 5, 6). The swelling of the cell and the nuclear changes, the alterations in the basophil Nissl substance is much more pronounced in the smaller cells of the cerebral cortex especially the small and medium sized pyramids (*vide* Plate I., fig. 1), numbers of these may be found with crumbling edges, ruptured cell walls and extruded nuclei; only a few of the large pyramidal cells are thus affected. These remarks apply to monkey's brains in

which a severe temporary anæmia has been produced. Examination of the spinal cord by Marchi method, the animal being killed ten days or more after the operation, reveals only comparatively a few degenerated fibres in the crossed pyramidal tracts. This proves that such marked changes as those shown (changes indeed which, if they were not controlled by restoration of function and absence of evidence of degeneration of their axons, might be termed degeneration) are really only functional.

Moreover sections stained for fibrils by Cajal method show the integrity of the essential fibrillary conducting substance.

The fibrils of the large psycho-motor neurons of three animals which were killed twenty-four hours after ligation of four arteries were examined by this method, and the fibrillæ of the dendrites could be traced up to the superficial layer of the cortex in the brains of the animals (two cats and a dog) (*vide* Plate II.).

This explains how it is that cortical excitation by faradisation evokes movements readily in these anæmic brains of temporarily demented animals and how it is that some powerful stimuli will arouse a purposeful cortical reflex response, *e.g.*, a cat that had all four arteries tied and took no notice of ordinary sensory stimuli, on the approach of a dog was aroused from its prone position and in an incoördinate manner attempted to scratch the animal (*vide* Plate II., figs. 1, 2, 3). Likewise a monkey four days after ligation of three arteries was in an absolutely demented condition with rigidity of all its limbs; on the approach of a cat was roused to attempt flight and showed that with a very strong instinctive stimulus that its cortex was not entirely devoid of conscious activity. Later no stimulus of any kind would arouse any response. Subsequent examination of this animal's brain showed the most profound bio-chemical changes in the cells of its cortex, corresponding to those produced by complete cortical anæmia (*vide* Plate I., fig. 3).

Excitation whether artificially induced by faradisation of the cortex, or by the injection of absinthe is associated

with a chemical process involving the taking-up of oxygen. Ehrlich and Horsley have shown that the cerebral cortex of an animal injected with methylene blue only pales when the excitation produces a motor response, and Dr. Leonard Hill, repeating this experiment on animals the brains of which had been rendered *almost* completely anæmic by ligation of arteries, found the cortex faintly stained blue, but that a pallor occurred when the stimulus produced a motor response, and, slowly, as the oxygen was renewed in the tissues by the still feeble arterial circulation, the colour returned.¹

Again if in a monkey the blood supply to the brain is so completely cut off as to render it inexcitable, the removal of a clamp on the carotid artery renders the corresponding hemisphere excitable and in about one minute a motor response can be obtained. On again clamping the artery the excitability diminishes, and in about one minute no motor response can be elicited even on very strong stimulation. Again in some experiments² which I performed with Professor Sherrington we found that compression of the spinal cord in the mid-dorsal region so as to indent the spinal cord did not interfere with the transmission of impulses by the pyramidal fibres, for on faradic excitation of the motor area in the monkey, movements were as easily evoked in the lower limbs as previously. If, however, very slight compression of the lumbo-sacral region were made, so as to interfere with the circulation in the grey matter, then the strongest excitation of the leg area ceased to produce any movement after about one minute. On removing the pressure so as to restore the circulation to the synapsis in the grey matter, the block to the passage of the stimulus was soon removed and in 1-2 minutes a current of moderate strength gave the normal response. *All these facts point to an oxidation process occurring at the terminals of the neurons of the motor path in the grey matter of the*

¹ "On Cerebral Anæmia and the Effects which follow Ligation of the Cerebral Arteries," by Leonard Hill, M.B., F.R.S., Philosophical Transactions of the Royal Society. 1900.

² These experiments were performed in 1895 and were referred to in my Croonian Lectures on the Degeneration of the Neurone, 1900.

DESCRIPTION OF PLATE II.

FIG. 1.—Large psycho-motor cell from the crucial sulcus of a cat showing the neuro-fibrils passing through the cell from the dendrons to the axon. Stained by Cajal method. Magnification 500 diameters.

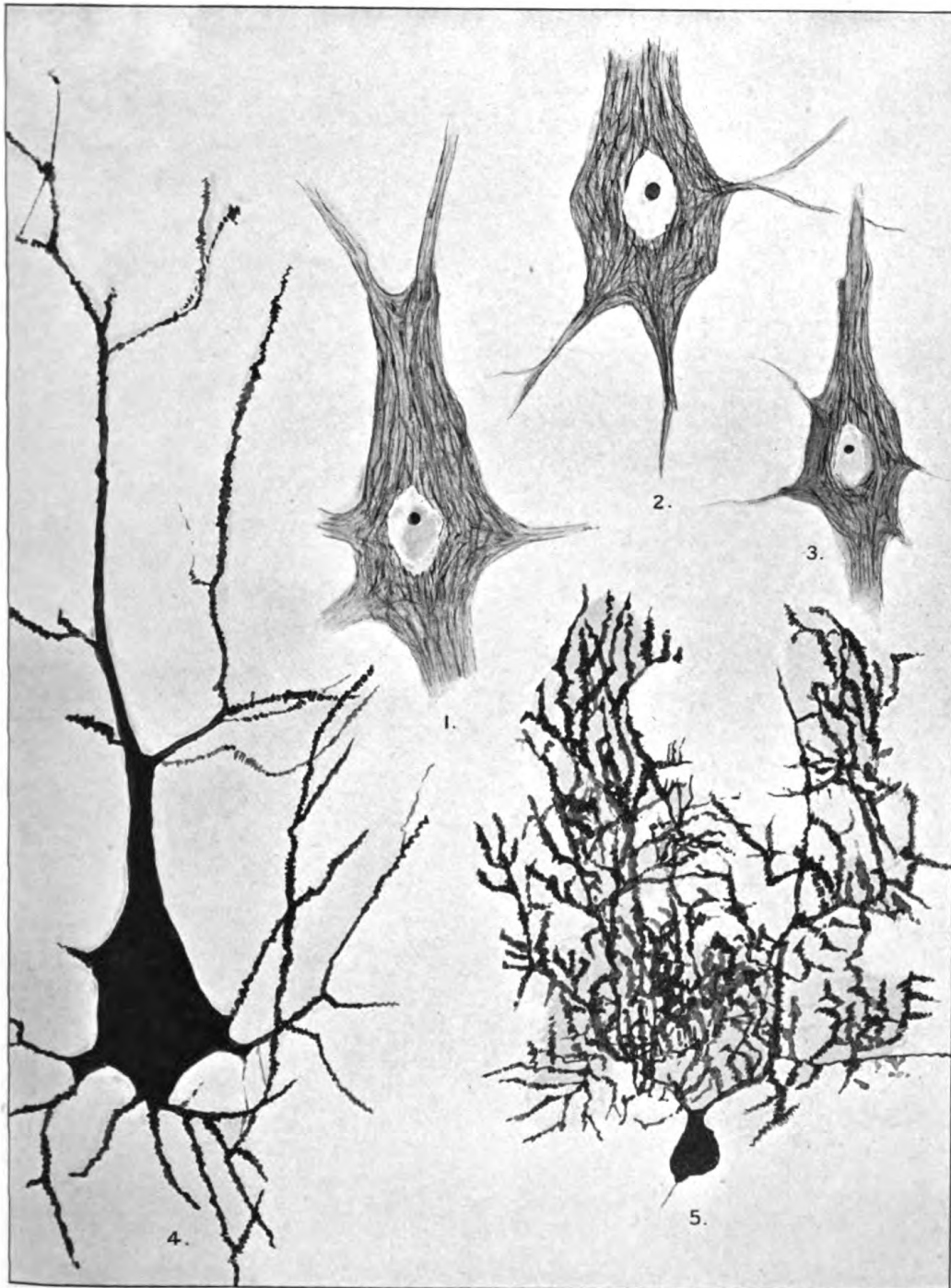
FIG. 2.—Ditto. Magnification 500 diameters.

FIG. 3.—Pyramidal cell from the same specimen. Magnification 500 diameters.

FIG. 4.—Pyramidal cell from the cortex of a monkey, five days after ligation of two carotid arteries and one vertebral artery. Stained by the rapid Golgi method, showing gemmules on the dendrons and all the external appearances of a normal cell. Magnification 500 diameters.

FIG. 5.—Cell of Purkinje from the cerebellum of a dog twelve days after ligation of four arteries, showing absolutely normal appearances. Magnification 190 diameters.

PLATE II.



cortex and the sub-cortical centres; and that the metabolic changes incidental to functional activity occur here where the vascular supply is most abundant. This chemical change is the source of mental activity.

Do the neurons when excited either by faradisation, or acted upon by convulsants in the absence of a sufficiency of oxygen, show changes which might be interpreted as indicative of fatigue?

Observation of sections prepared by Nissl method of the two hemispheres of a cat's brain rendered almost completely anæmic by ligation of arteries showed no recognisable difference in the appearance of the cortical cells of the two hemispheres. Although one had not been excited at all; whereas the other had been faradised at intervals for two hours.

But then from what has been previously said, no response is obtainable unless oxygen is used up. Then it may be asked how is it that the cortex remains excitable when the oxygen is so obviously deficient as compared with the normal.

The effect of excitation of the cortex is both excitatory and inhibitory on groups of correlative antagonistic muscles and it is probable that the reason a moderate, or even a weak current, with deficient oxygen and a proportional feeble chemical metabolic change, evokes a motor response, is that the impulse is purely excitatory and not in any way neutralised by inhibitory innervation currents.

The main expenditure of chemical energy in the cerebral cortex is concerned with inhibition, a function later acquired, and probably dependent upon the functions of cortical neurons of later ontogenetic and phylogenetic development (the layer of small, medium and large sized pyramids situated above the layer of granules), in which are revived the memory images of past experiences upon which we depend for judgment and volition. A layer which Bolton by a series of careful micrometric measurements has shown to be especially wasted in dementia and amentia.²

² Bolton. Histological Basis of Amentia and Dementia. Archives of Neurology. Vol. II.

In fact, there is a parallelism between the loss or deficiency of mind and the decay or deficiency of this layer. Moreover, in the brains of animals temporarily demented, as compared with the large Betz cells, the pyramidal cells are specially swollen and altered in their appearance, but probably the reason there is no longer the possibility of reviving memory images in these animals, is the lack of oxygen at the synapses of the terminals of the sensory projection system with the cortical association neurons.

The fact that the two kinds of change observed in the cortex as a result of ligation of arteries in great measure resemble the changes observed in toxæmic conditions support the conclusion that toxins act upon the neural elements in such a way as to functionally depress or abolish the normal metabolism.

Animals that died either within twenty-four hours, or never recovered from the demented and paretic condition, showed changes in the cortex quite different to those that recovered.

There is not merely chromatolysis and a physical change due to absorption of cerebro-spinal fluid causing a dropsical appearance of the cell, this may, or may not happen; more frequently in *complete* anæmia the cells are not swollen, but are even shrunken. The staining reaction is also different showing a bio-chemical as well as a bio-physical change has taken place. If a double stain of methylene blue and saffranin or if polychrome be used, the whole cell stains uniformly pink or dull purple and not with a brilliant differential colouration of the Nissl bodies and fibrillary substance as in the normal.

The condition is somewhat similar to that met with in hyperpyrexia, and identical with the appearances described by Sarbo* in the motor spinal neurons of the lumbo-sacral region after clamping the abdominal aorta.

A monkey which was killed five days after ligature of both carotids and one vertebral presented the most instructive changes; it was paretic and demented, took no notice of anything, and behaved exactly like an animal with its

* *Neurologisches Centrablatt*, 1895.

higher cortical centres destroyed. Examination of the brain of this animal exhibited the following changes shown in Plate I, fig. 3.

The ganglion cells and all their processes were uniformly stained a dull purple; the perivascular spaces were greatly dilated, the vessels empty, but there was little evidence of inflammatory reaction. Scattered through the protoplasm of the cells was a fine purple stained dust, the apical processes of many of the pyramids were destroyed or twisted like corkscrews; the dendritic processes were destroyed or swollen and irregular in form. Some ganglion cells could be seen in a state of advanced necrobiosis with phagocytic cells sticking to them. Although the Nissl method showed this profound change in all the cells of the cortex, yet the rapid Golgi method displayed numbers of pyramidal cells with gemmules on the dendrons and all the external appearances of a normal pyramidal cell (*vide* Plate II., fig. 4).

I mention this fact because it demonstrates the unreliability of all observations appertaining to mental states and pathological changes in the cortex in which sole reliance has been placed upon this excellent anatomical, but unreliable method when applied to the demonstration of cerebral lesions in toxic psychoses.

These results upon temporary and permanent dementia caused by temporary and complete anæmia of the cerebral cortex have the following important bearings upon the subject under discussion.

(1) Complete restoration of cortical function may occur provided collateral circulation is re-established before biochemical changes of coagulation necrosis occurs.

(2) The restoration of function in the transitory aphasias, word blindness, word deafness, monoplegias, hemiplegias and disturbances of consciousness met with in syphilitic endarteritis cerebri, is explained by a temporary anæmia occasioned by occlusion of an artery without spreading thrombosis occurring. Collateral circulation restores the function. Also the extraordinary recovery from seizures of general paralysis suggests that a portion of the

symptoms may be due to functional disturbance of the cortex brought about by circulatory derangements. A large number of the cortical cells in general paralysis show acute changes due, no doubt, to vascular disturbances. Many exhibit the swollen dropsical condition of functional change and, as the dog's anæmic brain shows, capable of recovery; others show the acute necro-biotic change, incapable of recovery and if psycho-motor in function giving rise to convulsions in the stage of irritation preceding death.

TWO CASES OF RAYNAUD'S DISEASE.

UNDER THE CARE OF DR. F. W. MOTT, F.R.S.

Physician to Charing Cross Hospital.

REPORTED BY JOSEPH EVANS, M.B., B.Sc.

Late Assistant Pathologist to the London County Asylums and formerly House Physician to Dr. Mott, Charing Cross Hospital.

(1) *A Case of Raynaud's Disease with Symmetrical Gangrene of the Finger-tips.*

THE patient was a farm labourer, aged 30, and admitted on November 25, 1904, for "bad hands."

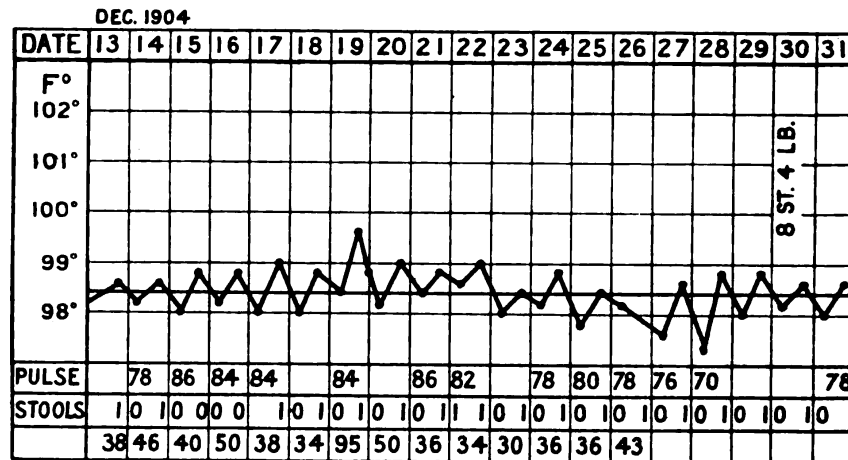
History of the Attack.—He said his hands were as usual until about three weeks before admission, when during a spell of rather cold weather his fingers had become "blue." He first noticed it in the index finger of his left hand, then in the index of his right hand. A little later all the fingers except the thumbs were affected. They also became painful and interfered with his work, some embrocation he used seemed to make them worse, and to make them swell. The pain gradually vanished but the finger tips were left "dead" and often had a "numb" feeling. About the time he suffered thus from his fingers, he had noticed his urine was "black" on two or three occasions.

He had not had a previous attack, denied syphilis, or any other disease. He had been a soldier and served in South Africa. His work as a farm labourer had included milking and carrying of milk-cans. He was not aware that the cows he attended had any disease. He had not been subject to "dead fingers" or toes. There had not been at any time blueness of ears or nose. The family history was of no significance.

Condition on Admission.—The right hand showed discolouration going on to superficial gangrene of the terminal phalanges of the index, middle and ring fingers, and slightly of the tip of the little finger; the discolouration extended to the middle of the second phalanx in the case of index and middle fingers, to the junction of the second and third phalanges in the case of

the third finger. There was considerable diminution of tactile sensibility in the second and third fingers. On the left hand there was superficial gangrene of the tip of the index and little fingers with discolouration of the tip of the ring finger. The thumb and middle fingers were intact. There was no confusion of sensory impressions on this hand. The tips of the fingers were soft, almost fluctuating, except that the left ring finger was extremely hard, and the palmar aspect of the terminal phalanx of the right middle finger comparatively so. The first phalanges of the right index and middle fingers were swollen slightly. The radial pulses were soft and small, the vessel especially on the right side a little thickened.

No abnormality of respiration, nervous or other symptoms could be discovered. His urine was normal.



(2) *A Case of Raynaud's Disease with Symmetrical Bullæ on the Hands.*

Course of the Case.—For a couple of weeks the condition of the fingers seemed to be stationary, so it was decided to let out the fluid which was obviously present under the cuticle of the fingers of the right hand and to cut away all dead tissue. This was duly done, and the removed tissue included the nails of the first and second fingers of the right hand. Fomentations were then applied every four hours and the tips soon granulated up beautifully; new nails rapidly formed and the slight loss of substance that had taken place was renewed. On the left hand no incisions were necessary and under hot boracic fomentations the thick gangrenous skin and subcutaneous tissue came away leaving fresh granulations in their place, which were quickly covered with healthy skin.

The patient was a footman, aged 17. He came to the hospital

on Monday, February 27, 1905, complaining of blisters on his hands.

History of his trouble.—He said he was in his usual health until Wednesday, February 22, when he noticed his hands were blue and swollen, but as he was subject to similar attacks it gave him no concern. On Sunday, February 26, he remembered feeling a little feverish in the evening and awoke the next morning with the blisters on his hands; he forthwith came to the hospital. He had been out of work and looking for employment for about ten days previous to admission, and possibly in consequence had been out of doors a little more than usual, but the weather had not been particularly cold.

Previous History.—He had rheumatism as a child, but no other special disease as far as he was aware. He was naturally healthy, but had always suffered severely from chillblains on his hands, feet and ears. As long as he could remember he had been liable to peculiar attacks of deadness in his arms and hands. In such attacks, his fingers, hands and arms, even as high as his shoulder, became first very white (corpse-like) and shrunken. They felt dead, were almost insensitive to touch, and stiff. After a while, the pallor would disappear and they became bluish and swollen, not uncommonly there were patches that looked dirty (mottled). As the attack passed off it was followed by aching pain like that experienced on exposure on a frosty day. There was no perspiration and the veins were not distended; as a rule the affection was not bilateral, one day it might be the left arm, the next the right arm, sometimes both would be affected simultaneously. The attacks usually came on suddenly and lasted about half an hour; he could not associate them with any particular task. On an average he had about two such attacks each week during the winter. Nothing comparable to gangrene had ever occurred. He had never noticed any blood or other peculiarity in his urine, and gave no history of melæna, hæmatemesis or hæmoptysis. He had never suffered from epilepsy, chorea, vertigo, or impairment of vision, there had been no wasting of muscles.

Family History.—His father had been a plumber and died of paralysis of the right side following "lead poisoning." There was no family history of insanity, epilepsy or any nervous disease. No one as far as he knew suffered with attacks like his.

Condition on Admission, February 27, 1905.—Patient is well nourished, fairly well built and with a fresh colour. The ears show signs of recent chillblains, they are bluish-red and the epidermis desquamating. The nose, tongue, and eyelids are normal. The hands are bluish-red in colour, markedly swollen and œdematous over the back, slightly swollen also on the palmar aspect. The swelling ceases gradually at the metacarpal phalangeal joint, they feel cold and show scars of broken chillblains on the ulnar side.

Detailed Description of the Right Hand.—Over the head of the second phalanx of the thumb is a discoloured patch of skin 3×4 mm.; over the head of the second metacarpal bone and covering the knuckle is a large blister; it is nearly circular, 15 mm. high, 40 mm. long, 30 mm. broad, filled with yellowish fluid and looks precisely like the blister of a burn. There is another small patch of discoloured cuticle on the inner side of the first phalanx of the forefinger, and other similar patches distributed over the knuckles and phalanges of the second, third and fourth fingers; these patches are very slightly raised, purplish in colour at the centre, yellowish brown at the periphery, gradually fading off into the rest of the skin. On the ulnar side of the fifth metacarpal is quite a large patch of skin in a similar condition, this includes a scar of an old chillblain, a brownish-yellow patch 15×6 mm. an irregular blister about 2 cm. long, 1 cm. wide and two dark purplish spots.

Description of the Left Hand.—The thumb is clear. Over the head of the second metacarpal and extending on to the knuckle is a large blister, but not quite equal in size to that of the right hand. In position, size and character it is strikingly symmetrical with that on the other hand. On the knuckle of the third finger is a small discoloured patch of cuticle like those already described; it looks very like an abortive blister. On the ulnar side of the fifth metacarpal is a discoloured area like that of the right hand, showing a brownish yellow area, 12×3 mm. long, and a larger purplish spot.

On both hands the nails are well kept and give no indications of malnutrition. Sensation (tactile, painful and thermal) is intact all over both hands. Movement of the fingers and wrist is good, except in so far as the blisters interfere with the movement of the forefinger.

The Feet.—The toes of both feet have a cyanosed appearance, especially on the left foot, the cyanosis extends well on to the outer side. There is no desquamation and no blister.

Sensory System.—There is no disturbance of sensation on any part of the body.

Motor System.—Normal. No incoördination.

Reflexes.—Normal, except that a plantar response can never be obtained in stimulation of the sole; the toes invariably extend and separate.

The urine is normal and contains no blood pigment.

The heart, kidneys and lungs, normal.

A blood count showed a full percentage of hæmoglobin, 5,000 leucocytes, 5,600,000 erythrocytes.

Progress of the Case.—On Saturday, March 4, the hands were far less swollen; the left was normal in size, but there was still

some swelling on the back of the right hand. No œdema. The large blister of the right hand had broken during the night. Nothing was done to the hands save to dress them aseptically.

The blister on the left hand looked very tense and was a little painful. A little of the fluid was withdrawn and an attempt made to grow cultures from it on blood serum; but after three days' incubation there was still no growth. The blister on the left hand broke on Sunday, March 5. By Wednesday, March 8, all the swelling had vanished, and the hands were rapidly assuming a normal appearance.

Patient left the hospital on March 15 perfectly fit, and with hands perfectly normal in size and colour. He had no hæmoglobinuria while in hospital and no attacks of local syncope or asphyxia.

FRONTAL TUMOUR SIMULATING GENERAL PARALYSIS

BY F. W. MOTT, M.D., F.R.S.

Case of large slow growing frontal tumour without manifest signs of intracranial pressure affecting specially the left hemisphere, giving rise to fits, unequal pupils, mental disturbances, reeling gait, slurred speech, in a man, the subject of chronic alcoholism. A diagnosis of general paralysis was made. Post-mortem: a large alveolar endothelioma with a large amount of dense fibrous tissue had destroyed the whole of the left frontal lobe, with the exception of the orbital surface, and had invaded the right frontal lobe, also.

William, T. C., age 38, occupation, stage carpenter; formerly stage manager. The patient, as he entered the out-patient's room at Charing Cross Hospital, attracted my attention on account of his physiognomy and dress. He had the appearance of a man who had been in better circumstances, who had taken to drink. His face was flushed and bloated; there were venules on his nose; he had a dull confused look. He was untidy in his dress; his shirt sticking out between his waistcoat and his trousers; he complained of feeling strange in his head, with a tight feeling across the forehead; and unlike his former self. He acknowledges that he had specific infection eight years ago. He has separated from his wife, but lives with another woman who passes for his wife. She gave me the following account of him:—He has had considerable worry owing to his being out of work, and he has for some time past drank heavily. He had had numerous fits, the first of which occurred five years ago, and have continued at intervals of two or three months since. She has no difficulty in managing him, but occasionally he is wet and dirty in his habits, and does not respond to the calls of nature. Frequently he forgets what he has done a minute or two before, and repeats himself over and over again. He does not appear to have had any delusions, illusions or hallucinations, although there is considerable mental confusion, and he rambles in his conversation. He has not suffered with severe headache or had vomiting; but he is often so dull and stupid that he is incapable of attending to anything; and she has noticed that his mental state has been progressively deteriorating.

Physical Examination.—The pupils are unequal and react sluggishly to light and accommodation; the discs show no obvious

signs of optic neuritis. There is slight tremor in the lips and tongue; and his speech is somewhat slurred and hesitant. The gait is unsteady and shuffling, and he walks and occasionally reels like a drunken man. The unsteadiness in station is not increased on shutting the eyes. The knee jerks are brisk on both sides. He was subsequently at my recommendation seen by Dr. Percy Smith, who confirmed the opinion that I had expressed, that the patient was suffering from progressive dementia of general paralysis, and he was sent to Cane Hill Asylum. The following notes were forwarded to me:—

W. C. Admission, November 26, 1902; died April 16, 1903. Stage manager, aged 39. Weight on admission 11 st. 8 lbs.; height 5 ft. 8½ ins.

History.—First attack: First fit, duration ten hours; cause, business worry and “epilepsy”; has suffered from fits for five years, chiefly in the early morning; has had some sort of “rash” on the body. [Lately has been attending Dr. Mott’s Clinic at Charing Cross Hospital.] Unsteady and intemperate. Married, but separated from wife. Living with a woman. No children. No family history of insanity, phthisis, or alcohol. Stated to have become grandiose of late.

Condition on admission.—In fair general condition, but pale and flabby; somewhat weak and ataxic in gait; tongue steady, slightly furred; hair brown; slight acne of face and back; irides grey; pupils dilated, almost fixed, and unequal (right larger); patellar reflexes present; no bruises or marks of injury; heart sounds faint; no further evidence of visceral disorder; articulation impaired; dull, rambling, and foolish; says he feels “strange in his head”; contradicts himself; memory much impaired; does not know where he has come from; says he has had fits recently, but cannot remember when or where.

December 17.—Continued in above state until December 17, 1903, when he had a slight hemiplegic attack affecting right side as far as could be ascertained; attack followed by great stupor. *December 19.*—No further seizure, but constant slight twitching of muscles of arms (both sides). *March 10, 1903.*—Becoming demented; wet and dirty in habits; articulation worse; stammers. *April 4.*—Slight seizure; no paresis of limbs. *April 16.*—Died at 6.35 a.m.

Post-mortem Examination.

Body well-nourished; no injuries; no bed-sores; skull-cap dense and fairly thick; dura healthy; no disease of bone. Brain forwarded to laboratory.

Ribs intact. *Heart* large; aortic and mitral valves both thickened, but competent; muscle friable. *Lungs*, left congested; right emphysematous; no tubercle. *Liver*, large white puckered scar on anterior aspect. *Spleen* small, fibrous. *Kidneys, intestine, &c.*, healthy.

Weights.—Brain, 53 ozs.; heart, 10½ ozs.; right lung, 20 ozs., left lung, 24½ ozs.; right kidney, 7 ozs.; left kidney, 8 ozs.; liver, 50 ozs.; spleen, 4 ozs.

Remarks by DR. DONALDSON.

The general symptoms of tumour were not present. The patient never complained of headache, and had no vomiting. An attempt at ophthalmoscopic examination was unsatisfactory, chiefly owing to patient's mental condition. Well marked mental torpor, progressive dementia, speech affection, and ataxic gait, fixed pupils, right larger than left. Diagnosis of progressive paralytic dementia was made, although it may be said that the attendant in charge of the case said he did not behave altogether like an ordinary general paralytic.

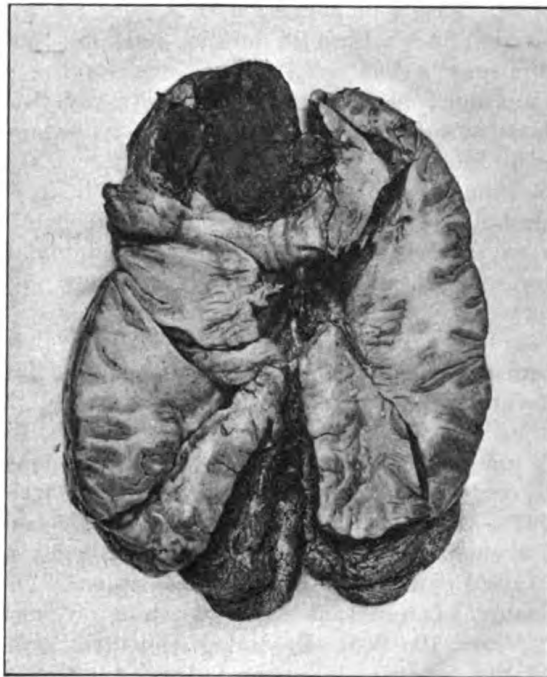


FIG. 1.—Tumour in the left frontal lobe, as seen after the tops of the hemisphere have been removed by a horizontal slice.

Description of the brain, after it had been preserved in formalin a few days, and forwarded to me:—Convulsions of the convexity were somewhat flattened. Occupying nearly the whole of the left frontal lobe is a dense hard fibrous irregularly nodulated new growth, which has invaded the surface of the convexity to such an extent as to have completely destroyed the superior frontal convolution for three inches, and partially the second frontal. It has destroyed the mesial surface of the frontal lobe entirely, with the exception of a thin layer,

continuous with the orbital surface of the lobe. The tumour is as large as an orange, but it is of an irregular shape and consists of two large lobes, which are however continuous. The surface of these lobes are irregular with nodes and nodules of varying size from a small marble to a millet seed. It lies in a cavity formed by the brain substance out of which it can be shelled readily. The floor of the cavity is formed by the orbital convolutions and on lifting it out there is a thin layer of blood exudation. The external lobe is just coming to the surface, and has invaded and

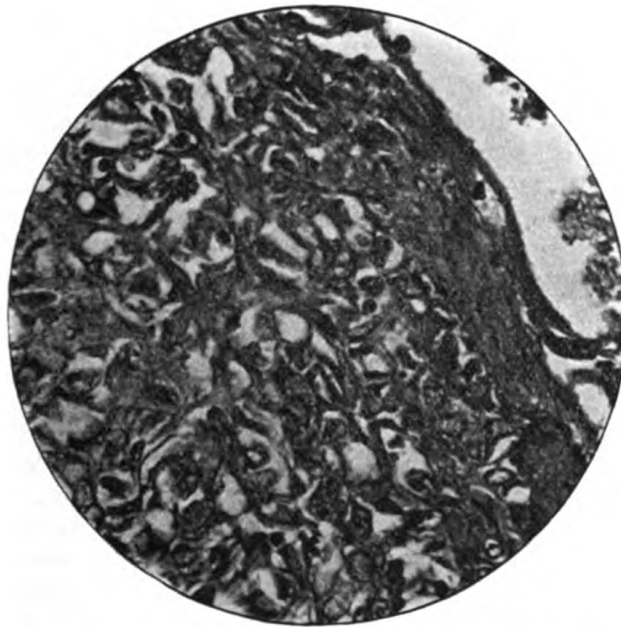


FIG. 2.—Section of the tumour showing irregular-shaped epithelial cells contained in alveolar spaces, formed by a dense and abundant fibrous reticulum. Mag. $\times 280$.

partially destroyed the base of the inferior frontal convolution of the left hemisphere; and this accounts no doubt for the speech affection. It has not invaded the ascending frontal, or the pars basilaris. Hence there was no facial paresis and no aphasia. There was no indication in the specimen received as to where the growth commenced. Microscopically examined the growth was found to be an alveolar endothelioma. There was a large amount of dense fibrous tissue between and around the alveoli, which accounted for its hard and dense consistence and its slow growth. It was not highly vascular. The alveoli contained small irregularly shaped endothelial cells.

Remarks.—The growth probably started from the falx cerebri, and was of duro-matral and arachnoid origin. I judge this because the greatest amount of destruction was on the mesial surface. Moreover it commenced to invade the opposite frontal lobe. The absence of the general signs of tumour, vomiting, severe headache, and optic neuritis may probably be accounted for by the fact that the tumour slowly invaded and destroyed the brain tissue, and consisting largely of fibrous tissue, was therefore not highly vascular, and did not give rise to marked increase of intracranial pressure. By its proximity to the motor area it gave rise to irritation and fits, without causing paralysis; to slurred and hesitant speech without aphasia or facial paralysis, and to ataxy from the invasion of the structures of the frontal lobe which are connected with the opposite lobe of the cerebellum. The unequal pupils and the effects of the alcohol combined with the speech affection, and the absence of signs of intracranial pressure, led experienced observers thus to a wrong diagnosis, which is regrettable; seeing that the patient came to a general hospital, and if it had been diagnosed the tumour could have been successfully removed by an experienced surgeon.

CASE OF SEVERE INJURY OF THE FRONTAL
REGION OF THE BRAIN FOLLOWED BY
MENTAL CHANGES IN THE FORM OF LOSS
OF HIGHER CONTROL.

BY ROBERT JONES, M.D., F.R.C.S., M.R.C.P.

Superintendent of Claybury Asylum.

THE consensus of opinion to-day supports the view advocated by Bechterew and Francesco Durante that the frontal lobes, more especially the prefrontal, are the seat of the highest functions of the mind, and the following case the result of a severe accident to the right frontal lobe may therefore be worthy of record as supporting this view.

X.Y., aged 26, single, height 5 ft. $2\frac{1}{2}$ ins., weight 8 st. 5 lbs., well educated, of fair complexion, was admitted into Claybury Asylum from prison.

Family history.—Father and mother are country-born, Herts and Berks., respectively. Maternal grandparents lived to 82 and 83. Paternal grandparents were healthy. No insanity on either side. Mother had two sisters and three brothers, no insanity, and all abstainers. Father had two sisters and two brothers, all living, no insanity. Patient has two sisters and three brothers, all living and healthy.

State on admission.—There was nothing abnormal in the state of his heart, the pulse wave was of fair tension, and regular. He was of fair muscular development and his reflexes were normal. There was no disturbance of sensation and no difficulty about the erect position or his gait. The pupils were equal, 3 mm., they reacted equally to $2\frac{1}{2}$ mm. in ordinary light, and to 2 mm. in bright light, they also reacted to accommodation. There was natural convergence and deviation. He complained that since the accident his sight had become impaired, as he is unable to see clearly at long distances. The discs were somewhat paler than normal. Urine 1,020 acid, no albumen and no sugar. The patient presented an irregularly depressed linear scar, six centimetres long, vertically across the forehead. It was about five centimetres to the right of the middle line and extended upwards through the right side of the bridge of the nose, being five centi-

metres in depth in the deepest place. The right frontal bone was obviously depressed and the skin was scarred over it. The circumference of the head was 22 inches. His mental state on admission was that of organic dementia secondary to injury of the brain. His memory was greatly impaired. He was unable, within a period of three years, to localise in time the date of his accident. He confessed to being led away by his feelings against his will, and to be deficient in self-control. He also said that his great pleasure was attending religious meetings and it was chiefly on such occasions under the influence of religious excitement that irregularities in his conduct occurred. He states that he prefers being alone,



that he is worried in society and loses his temper. He further admits that his home and those previously dear to him lost their attraction for him. He appears to have, at present, no consideration for others. He had the delusion that people in the streets spoke of him, that they made signs and annoyed him by talking over his affairs and he felt himself watched. He seemed to be weakened in intellectual powers and he had no recollection of the crime which caused him to be imprisoned. He is certainly most shameless about his misdeeds.

Previous history.—Until the age of 21 and up to five years ago, he was an abstainer, and had been engaged as a responsible hand in the Inspection Branch of the Receiving Stores at the

Government Royal Dockyard, Woolwich. He met with a serious accident, falling a distance of over forty feet down a lift, through the bursting of a hydraulic cylinder. He was picked up unconscious and remained so for several days, having fractured his skull, and sustained a serious injury to the right frontal lobe, some brain substance having escaped through the wound. He was conveyed into the Government Hospital where he remained for about two months; about four months afterwards attending at St. Bartholomew's Hospital, London, where portions of dead bone were removed from the wound. He was under the treatment of the Royal Army Medical Corps intermittingly for about two years, and when sufficiently well was given some light work to do, but he was found to be of no use, and eventually—about two and a half years after the accident—he was pensioned. Up to the time of the accident he was bright, active, energetic and trustworthy. He was a life abstainer and a Sunday-school teacher. He was apparently forging his way to the front—gaining the respect of his employers, and giving general satisfaction. After the accident however, there is a record of gradually increasing moral obliquity and mental infirmity. During this period he has been three times convicted of indecent behaviour; on the first occasion (two and a half years after the accident) he was fined; on the second, in May, 1905, he was bound over, and on the last occasion, January, 1906, he was found guilty, but insane, and was sentenced to be detained during His Majesty's pleasure.

He was a month in prison before his admission into Claybury, during which time he showed no suicidal nor dangerous tendencies. He did not appear to realise his position, nor the wrongful character of his actions—of which he talked freely and shamelessly, and he apparently thought his offence was a very slight one. In prison he also imagined that people followed him about and talked of him and of his affairs and this was looked upon as an insane delusion. His mother states that since the accident, he has appeared to get gradually weaker in his mind. He became careless of himself and his appearance, and he has not been so sharp and quick. He has not applied himself to anything to help his livelihood, but wandered about aimlessly, sometimes staying out all night. His temper became irritable and violent, and his mother went about in fear of what he might do to her. He became odd in his ways, could not fix his attention on anything. For some time after the accident he could not stand because as his mother thought "he got so very weak." She summed up her account of him by saying that "the accident seemed to have changed him in every way."

Colonel Z., Royal Artillery writes: "In my opinion X.Y.'s character has altogether changed by the injuries received. From being a steady, honest, reliable man he became in every way

the reverse, and I have always considered that since the accident he has not been responsible for his actions and should have been put under restraint (this letter was written previous to his coming into the Asylum), but of course it was difficult to prove this. I may add that from time to time I saw a good deal of him and had many opportunities of forming an opinion."

This case is of interest although we possess no definite knowledge of the exact extent and amount of destruction of the brain; but the history shows clearly that a frontal lobe injury was followed by a marked change in character, and in this respect it is of interest to compare the notes of this case with the notes of the celebrated American "Crowbar Case": A young man was hit by a bar of iron $1\frac{1}{4}$ inches in diameter, which traversed the anterior part of the left hemisphere, going clean out of the top of his head. This man lived for thirteen years without any permanent alteration of motor or sensory functions; but the man's disposition and character underwent a serious change as the following report shows:—

AMERICAN CROWBAR CASE.

Report of Dr. Harlowe, under whose care the patient came immediately after the accident: "His contractors, who regarded him as the most efficient and capable foreman in their employ previous to his injury, considered the change in his mind so marked that they would not give him his place again. The equilibrium or balance, so to speak, between his intellectual faculties and animal propensities seems to have been destroyed. He is fitful, irreverent, indulging at times in the grossest profanity (which was previously not his custom), manifesting but little deference for his fellows, impatient of restraint or advice when it conflicts with his desires, at times pertinaciously obstinate, yet capricious and vacillating. . . . A child in his intellectual capacity and manifestations, he has the animal passions of a strong man. Previous to his injury, though untrained in the schools, he possessed a well-balanced mind, and was looked upon by those who knew him as a shrewd, smart, business man, very energetic and persistent in executing all his plans of operation. In this regard his mind was radically changed, so decidedly that his friends and acquaintances said he was 'no longer Gage.'"—"The Present State of Mental Science," Bernard Hollander, *Journal of Mental Science*, April, 1901.

CASE OF CEREBRAL TUMOUR ILLUSTRATING THE DIFFICULTY OF LOCALISATION.

BY F. W. MOTT, M.D., F.R.S.

Early symptoms of optic neuritis followed by blindness. History from friends of the character of the fits suggesting that the tumour was situated in the left hemisphere, causing irritation of the right motor area. Sent up for operation, which was not performed owing to the very indefinite character of the localising symptoms. Large tumour in the temporal lobe discovered, post-mortem, which accounted for certain slight signs observed while the patient was in hospital, notably partial obliteration of the left naso-labial fold.

M. L., female, aged 24. Cook. Admitted under my care at Charing Cross Hospital, September 20, 1905, for cerebral tumour.

Abstract of Notes.—Illness began eight months ago with failure of her eyesight; a mist seemed to come in front of her eyes; there were no hallucinations, no diplopia, no loss of colour sense; finally in about four months she became totally blind. During this time she suffered with attacks of severe headache, two or three a week. They usually begin about midnight and last all night and the following day. They are worse when she lies on her back. The pain is sharp and shooting, and affects the frontal region. Since the headaches have developed she has been subject to attacks of severe vomiting, usually one a week, lasting about twenty-four hours. They have no relation to food. The headache preceded the blindness two or three months.

There is nothing noteworthy in the family history, nor could any cause of her illness be ascertained, although since she fell out of a cart six months ago (probably owing to a fit) and cut her right eye, she has been worse.

One week before admission, according to the statement of patient's brother, she had a fit. The head and eyes turned to the right, convulsive movements occurred in the right arm and the right side of face was drawn up; afterwards the convulsions were general; she lost consciousness for about a quarter of an hour, and bit her tongue. She always complained of the pain in the head being on the left side, and used to put her hand to the left side of the head. The sister said that the patient complained of pins and needles in the right arm and hand, and she had con-

traction of right arm and right side of the face. The patient did not lose consciousness (when the sister saw an attack), and there was no lateral deviation of the eyes and head. She lost sight in left eye first. She was put upon 15 grains of iodide of potassium three times a day.

Physical Examination.—There is apparently some exophthalmus of the right eye, the left palpebral fissure is smaller than the right. Both optic discs pale and slightly swollen, margins ill defined, retinal arteries small. Post neuritic atrophy. Slight divergent strabismus and nystagmus on extreme movement of eyes to either side. Left eye slightly higher than right. No swelling palpable in the orbit. No sense of resistance on pressure backwards in the orbit.

Report of E. T. COLLINS.

There is no tenderness of the skull on percussion. There is no motor or sensory impairment to be observed. The superficial and deep reflexes are not exaggerated. There was nothing abnormal found in the cardio-vascular and respiratory systems, and the abdominal viscera were apparently unaffected. The temperature was normal. The only objective sign, beside the ocular phenomena described, was a partial obliteration of the naso-labial fold on the left side. The tongue protrudes in the mid line. There are no tremors.

Later, fits and vomiting occurred at intervals, but the precise manner in which the fits began was not observed; they were thought to be general. A weakness of the left hand was observed, and on November 10, 1905, it was noticed that the tongue deviated to the right, and the eyes turned in the same direction. The left pupil was larger than the right.

November 8, 1905.—Patient has the delusion that she goes for a drive every evening. She tears up the sheets to make reins, and when given bandages attached to the foot of the bed she takes them in her hands and thinks she is driving. She knows where she is, and also the time of the day, but is always asking for her dinner.

November 21, 1905.—The following notes were made. At 12.20 to-day, patient had a fit whilst being fed. Both arms and legs were extended, and then clonic spasms occurred in the arms and the legs. The patient was quite unconscious. No corneal reflexes obtained. The eyes deviated to the right. At intervals similar fits occurred.

December 7, 1905.—Incontinence of fæces and urine, fits of screaming, no doubt due to pain. She is more drowsy.

December 28, 1905.—Vomiting followed by a fit. Convulsions occurred on the right side, the left side was motionless, apparently paralysed. Pulse very feeble. Death from heart failure.

Post-mortem.—A large tumour mass was found involving nearly the whole of the temporal lobe on the right side. The tumour has led to considerable increase in size of the hemisphere. After hardening in formalin, the brain was cut in sections sagittally and a large vascular growth with disseminated gelatinous colloidal mucus in it, surrounding the upper portion, was seen. The growth has invaded both the corpus striatum and optic thalamus, especially the former, pushing them inwards so as almost to obliterate the lateral ventricles; it has extended forwards into the white matter of the frontal lobe, and partially destroyed the anterior half of the internal capsule. It does not appear to have invaded the posterior half of the internal capsule. It has not invaded the cortex of the temporal lobe except at the tip, but it has destroyed the greater part of the white matter of this lobe, and the island of Reil extending into and partially obliterating the claustrum. To the naked eye the spinal cord, after hardening in formalin, showed degeneration of the posterior columns.

Remarks.—There was no difficulty in diagnosing a tumour of the brain, but the signs and symptoms were far too contradictory and vague to allow of it being localised, and although the friends of the patient were most anxious for an operation to be done, and although the circumstantial evidence of the brother and sister pointed to a tumour near the motor region of the left hemisphere, the signs and symptoms exhibited by the patient when under observation did not support their statement, for the weakness of the left naso-labial fold and the prominence of the right eye suggested a tumour of the right hemisphere, probably basal. It was thought it might be a frontal tumour of the left hemisphere and this would have possibly accounted for the deviation of the eyes to the right; against this, however, was the fact that there was no speech affection, and the optic atrophy and blindness was one of the earliest and most prominent signs and symptoms. It was fortunate that the friends' wish was not complied with. Had the patient not already become blind, the skull might have been trephined for relief of intracranial pressure and to prevent blindness; but this is one example of many illustrating the difficulty of localisation, consequently the inadvisability of recommending surgical interference.

Her mind was little impaired; such impairment as existed could be explained by the increased intracranial pressure, the blindness and the hypnotics which were administered.

DIPHThEROID ORGANISMS IN THE THROATS OF THE INSANE.¹

BY J. W. H. EYRE, M.D., F.R.S. EDIN.

*Bacteriologist to Guy's Hospital and Lecturer on Bacteriology in the
Guy's Medical and Dental Schools.*

AND

J. FROUDE FLASHMAN, M.D., B.SC.

*Pathologist to the Lunacy Department, New South Wales, and
Honorary Demonstrator in Neurology and Tutor in Psychological
Medicine in the University of Sydney.*

THE pathological investigation of insanity in the past has chiefly had for its aim the determination of the histological changes caused by attacks of mental disorder. The results of such investigations have been many and important, but it cannot, we think, be claimed that these results have placed the clinician of to-day in a very much more favourable position than his *confrère* of twenty years ago.

But had the workers in the domain of general pathology been content to rest satisfied with the results obtained by histological methods alone, it is plain that most of the modern methods at the disposal of the progressive physician would have remained undiscovered. It is, therefore, not only reasonable, but absolutely imperative, that every new means for pathological research should be adopted by those whose particular work it is to investigate the etiology of mental diseases.

In the past we have been accustomed to think of insanity as a spontaneous breakdown of the nervous system due, for the most part, to a bad nervous heredity ; and so it may be, but until we can assert without fear of contradiction that all the causes of the great bulk of insanity have been sought

¹ The subject matter of this Paper was communicated to the Section of Pathology at the Annual Meeting of the British Medical Association, Leicester, July, 1905.

out and classed as unavoidable, it is the bounden duty of investigators to seek in every reasonable direction for causes which may be avoidable or removable.

Those, therefore, who are seeking by bacteriological or chemico-pathological means to discover a bacterial or toxic exciting cause for these diseases, occupy an unassailable position, and the work of Dr. Ford Robertson (with which we are at the moment concerned) entitles him to a place amongst the foremost of investigators pursuing this line of research. Dr. Robertson's many recent papers have pointed to the idea that a member of the diphtheria group of organisms—possibly¹ the Klebs-Löffler bacillus itself—may play an important part in the production of a great class of insanity—namely, general paralysis of the insane. His hypothesis is, we gather, that by syphilis, and perhaps other diseases associated with alcoholic excess and meat diet, the defensive powers of the organism are so reduced in certain directions that the individual falls a prey to the destructive action of the diphtheroid organism, which, he contends, is almost constantly associated with this class of insanity; and, further, that it is this organism or its toxin which gives the paralytic aspect to the disease.

On the other hand, he recognises that this bacillus is also present in the throats and other tissues of cases of insanity not having a paralytic character. That these cases do not show paralytic symptoms is probably due, he explains, to the fact that the defensive powers have not been reduced by preceding attacks of syphilis, &c. This, we believe, fairly states Dr. Ford Robertson's position.

OBJECT OF THE PRESENT INVESTIGATION.

This hypothesis by its novelty, combined with the weight of the carefully-thought-out arguments Dr. Robertson brings to bear upon it, is an extremely attractive one, and the issues involved are far-reaching and important. We there-

¹ In the Morrison Lectures Dr. Ford Robertson claims to have isolated a specific diphtheroid organism which he terms "*Bacillus paralyticans*." *Review of Neurology and Psychiatry*, 1906, vol. iv., February, March, April (Editor's Note).

fore determined to investigate the conditions that obtain in some of the large asylums south of the Tweed, with special reference to the relative frequency of the presence of a diphtheroid organism in the throats of the insane, and particularly of general paralytics; and, further, to examine such fluids and tissues as were easily obtained from the cadaver of the general paralytic at the *post-mortem* inspection, with a view to the detection of diphtheroid organisms.

The investigation appeared to us to be eminently desirable in view of the possibility that the facts hitherto observed might not warrant the inferences drawn from them. We hoped that our inquiry might throw some light on the question of whether Dr. Ford Robertson had to do with a "local infection" in the asylum from which he drew his material, or whether his results in this particular held good in the case of other asylums.

In the course of our investigations we have examined 138 living cases and material from 33 *post-mortem* inspections, with a great amount of care, and have subjected those organisms which we were able to isolate to fairly critical tests. Our material has been drawn from two asylums—the one, the London County Asylum at Colney Hatch, an old-established institution; the other, the London County Asylum at Claybury, a comparatively new one. The *post-mortem* material was obtained exclusively from Colney Hatch Asylum during a period of three months ending December 31st, 1903.

And in this connection we wish to express our thanks to Dr. Mott, F.R.S., at whose instigation the investigation was undertaken, and to whom the writers are indebted for much valuable advice and criticism. Also to Drs. Seward and Jones, the medical superintendents of the Colney Hatch and Claybury Asylums respectively, as well as to the medical staffs of those institutions, for so freely placing clinical material at our disposal.

As a preliminary, we deemed it advisable to ascertain the opinion of others as to the degree of frequency with which "diphtheroid" organisms could be detected in the throats of normal individuals under varying conditions. With this aim

in view we have referred to a number of papers by different workers which appear to bear upon the question, and which have been published during the last decade—for we considered that by restricting ourselves to comparatively recent literature we should be able to include results in which attempts had been made to differentiate between the *B. diphtheriæ* of Klebs and Loeffler on the one hand, and other members of that large class of organisms (including the bacillus of Hoffmann) loosely grouped under the term “pseudo-diphtheria bacillus” on the other.

The results of our search, when averaged, showed that the true diphtheria bacillus may be isolated, by suitable means, from the throats of nearly 7 per cent. of the presumably healthy population. On the other hand it is found, when examining the throats of “contacts” (that is, of individuals in more or less close contact with actual cases of diphtheria) that this percentage rises to 33 or more. The authors consulted and the various figures obtained in this connection deal with observations upon nearly 10,000 individuals; and may be conveniently presented in the accompanying tabular synopsis (Table I.).

TABLE I.
THE INCIDENCE OF *B. Diphtheriæ* IN THE NORMAL THROAT.

Name	Total number investigated	Number of contacts	Percentage K.L.B. in contacts	Percentage Hoffmann's in contacts	Number of non-contacts	Percentage K.L.B. in non-contacts	Percentage Hoffmann's in non-contacts
(1) Cobbett, Louis ⁴	650	650	19·0	23·0	—	—	—
(2) Berry and Washbourn ² ..	118	118	14·4	19·4	—	—	—
(3) Goadby ⁸	686	586	32·4	16·0	100	18·00	16·0
(4) Gorham ¹⁰	2,375	1,406	11·9	—	969	3·00	—
(5) Kober ¹¹	723	133	84·0	—	590	15·00	—
(6) Massac. Board of Health ¹² ..	4,250	—	—	—	—	3·00	—
(7) Meade, Bolton ¹³ ..	214	214	45·0	—	—	—	—
(8) Müller ¹⁴	100	—	—	—	100	6·00	—
(9) Parke and Beebe ¹⁵ ..	378	48	50·0	—	330	9·77	7·2

In striking contrast to the results obtained by the above observers, we find, on analysing Dr. Ford Robertson's papers, that diphtheroid organisms were obtained *post*

mortem from one or more situations in 85 per cent. of a total of twenty general paralytics he examined. Of these diphtheroid organisms we gather that he considered all were true diphtheria bacilli. A percentage incidence such as this, if it can be shown to hold good generally, certainly affords grounds for the assumption that the association of general paralysis and the Klebs-Löffler bacillus is not a mere coincidence.

TECHNIQUE ADOPTED.

(a) *Material obtained during life.*—The methods we employed for obtaining and examining our specimens may be referred to in some detail, for so much of the value of observations of this character depends upon matters of technique.

The apparatus employed for the collection of material from the throat consisted of a simple "swab" similar to that used by one of the writers for cases of suspected diphtheria for many years past. This is prepared by twisting a small piece of cotton-wool around one end of a short metal rod and placing this, wool downwards, in a clean test tube. The tube is plugged with cotton-wool, and the whole placed in a hot-air steriliser at 150° C. for an hour to ensure complete sterilisation.

In collecting the material a swab was removed from its tube and the cotton-wool-covered end pressed firmly against several different points of the fauces (special attention being directed to the surface of the tonsils, and particularly to any purulent collections in tonsillar crypts) and of the back of the pharynx, rotating the metal rod at the same time between the thumb and forefinger. The swab was then replaced in the tube and the latter replugged and labelled.

Attention was also directed to carious teeth and swabbings made therefrom, but care was taken to prevent contact between the swab and either the tongue, palate, or the inner side of the cheeks.

The next step was to inoculate culture tubes (containing blood serum inspissated in the slanting position) "in series,"

by rubbing the swab firmly all over the sloped surface of the medium in a first tube; passing a sterile platinum loop over the inseeded surface of the serum in this tube, and with the material collected in the loop inoculating the surface of the medium in a second, and, finally, a third tube. By following this procedure, a large number of the organisms in the throat are rubbed on to the surface of the serum in the first tube; by means of the loop a few of all these organisms are conveyed to the second tube, and still fewer to the third tube. The tubes were then incubated at a temperature of 37° C. overnight, and examined early next morning—a period of about twelve to sixteen hours, never more than eighteen hours.

After incubation, the resulting growth on the first tube was usually a fairly even, moist layer over the surface of the medium, in which no discrete colonies could be distinguished. In the second tube the growth was decidedly less luxuriant, and some separate colonies were frequently apparent. In the third tube, however, the growth was always sparse, and consisted of discrete, scattered colonies from which subcultures could easily be made.

Coverslip films were then made from the abundant growth in No. 1 tube, a loopful of organisms being obtained by drawing the loop along the whole length of the sloped surface of the serum. These film preparations were then stained by carbolic methylene blue (thoroughly matured) and by Neisser's method, and examined microscopically, using the $\frac{1}{8}$ in. oil immersion objective. At the commencement of the work we also examined film preparations made direct from the swab and stained by similar methods. We soon, however, discontinued this form of examination, for, like preparations direct from swabbings of suspected diphtherial throats, the results obtained were by no means commensurate with the trouble and labour involved. In the Neisser-stained preparations the films were exposed to the action respectively of the acid methylene-blue solution and the bismark-brown solution for considerably longer periods than the few seconds originally suggested. This prolongation of the staining process was early recognised

as necessary by Neisser himself, and has been generally adopted in this country. Beaton, Caiger and Pakes,² in a paper dealing with the examination of throat material, have suggested a two minutes' immersion in each staining fluid, and this was the modification of the original method we employed in our work.

The detection, when present, of bacilli belonging to the diphtheria group, in which we include *B. diphtheria* (Klebs-Löffler bacillus), *B. xerosis*, *B. Hoffmanni*, *B. segmentosus coryzae* and other unnamed but allied species, by microscopical examination presented but little difficulty in that the writers have had considerable experience in the microscopical examination of cultivations from swabbings taken from cases of suspected diphtheria—an experience, in the case of one of us, extending to over 20,000 such examinations during a period of more than ten years.

The organisms detected microscopically were further differentiated into Klebs-Löffler bacilli, Hoffmann's bacilli, and diphtheroids (that is, some one or other of the remaining members of the group), and the complete diagnosis recorded. In only one instance has it been found necessary, after fully working out the life-history of the bacillus in question, to alter the diagnosis first made. The one exception relates to the bacillus isolated from the throat of Steward, and which, after a complete study, was found to be identical with the non-pathogenic diphtheroid bacillus isolated from a specimen of cow's milk, some years ago, by one of the present writers.⁶

And we may here remark that the differential diagnosis of these diphtheroid bacilli was invariably made on the result of the examination of the methylene-blue stained specimen derived from the blood-serum cultivation, as we are of opinion that the Neisser-stained specimens afford no information beyond that given more obviously and conclusively by the methylene-blue preparation. The value of Neisser's stain, moreover, is detracted from by the fact that quite 50 per cent. of the strains of diphtheroid bacilli other than the true diphtheria bacillus will, when examined under the conditions laid down as to age, medium, &c.,

show polar granules identical in appearance and situation with those originally considered as pathognomonic of the Klebs-Löffler bacillus (see also Table VII.).

Then, too, the streptococcus longus—a common inhabitant of the throat—and especially that rapidly-dividing form often met with, and dignified by some observers by the title “bacillary” form, will occasionally give appearances indistinguishable from those presented by the Klebs-Löffler bacillus, and these examples might easily be multiplied. On the other hand, species of *B. diphtheria* are often met with which, although typical as to morphology, cultural characters, bio-chemical reactions, and pathogenesis, fail to show the “Neisser’s stain,” even in the culture first obtained from the human body. The application of Neisser’s method as an aid to diagnosis has had a somewhat fictitious value attached to it as the result of the observations of Beaton, Caiger and Pakes,² already referred to, in that they used this method only and their results were not controlled by a competent observer working only with methylene-blue stained specimens, except in forty of their cases, and further, that all the cases examined were cases admitted to the hospital and under treatment there for diphtheria. Again, we are inclined to think that many of the twenty-five cases recorded as diphtheria clinically, but in which they were unable to detect *B. diphtheria* by the aid of Neisser’s method, would probably have given positive results if “methylene-blue” specimens had been prepared as well. This opinion is based on the results obtained in the Bacteriological Department of Guy’s Hospital, which show that fully 20 per cent. of the stains of true *B. diphtheria* do not give a positive result with Neisser’s method, although typical culturally and in point of virulence.

Mervyn Gordon,³ too, lays great stress on the differential value of the Neisser staining of bacilli isolated from the throat; but the observations on which he bases his conclusions are too few to need any comment.

Next, in those cases where a diphtheroid organism was recognised an attempt was made to isolate it. Occasionally

our efforts in this direction failed owing to the small number of this organism, and the enormous number of other organisms present in the specimens. In those cases where no diphtheroid organisms could be detected after examining numerous methylene-blue films in this way from the first tube of the series, the second tube was subjected to the same process.

Whenever a diphtheroid organism was detected microscopically in the films, a careful search was made in the second and third tubes—where the growth was naturally less profuse—for isolated colonies, or for spots where the diphtheroid organism was relatively abundant. Occasionally a pure colony was found; when this happened it was transferred to a fresh serum tube and a pure culture thus obtained. In other cases the organism sought was so mixed up with others that it was necessary to use plate cultivations in order to obtain a pure culture, and for this purpose the following method was adopted: A loopful from the most likely spot on the serum tube cultivation (as tested microscopically) was emulsified in 5 c.cm. of sterile broth, and two or three loopfuls of this emulsion were then rubbed over the surface of a "serum" plate (that is, about 15 c.cm. bullock's serum, inspissated at 80° C. in an ordinary petrie dish) by means of the short arm of a previously sterilised L-shaped glass rod. Without recharging or further sterilising, this rod was immediately rubbed over the surface of a second and then a third plate. The few organisms adhering to the rod after rubbing the loopful of broth over the surface of the first plate were thus deposited on these latter plates, and after incubation in the ordinary way, usually yielded a scanty growth of discrete colonies among which pure colonies of the diphtheroid organisms were sought.

Pure cultures having been obtained by one or other of the methods described above, the bacilli thus isolated were fully studied in parallel series with authenticated controls of the three chief members of the diphtheria group—namely, *B. diphtheria* (two varieties), *B. Hoffmanni* and *B. xerosis*—as to their (1) morphological characters; (2)

staining reactions; (3) cultural appearances and chemical activities; and (4) pathogenesis, and their identity finally established after a careful consideration of all these points.

With regard to the first of these—the morphological appearances—we have already expressed the opinion that these are sufficiently characteristic to warrant a correct diagnosis in the majority of cases if specimens are prepared from eighteen-hour old blood serum cultivations and stained with thoroughly matured carbolic methylene-blue. At the same time we sought further confirmation from the examination of microscopical preparations made from cultivations upon other media. Of such preparations, those made from cultures on alkaline potato incubated for thirty hours at 37° C. were undoubtedly the most hopeful; for on this medium the presence of enormous clubbed forms,¹⁵ either evenly or faintly stained, or showing bars of deeply stained protoplasm, readily differentiates the true diphtheria bacillus from the bacillus of Hoffman and other members of the diphtheria group whose growth on this medium is characterised by oval and spherical involution forms and coccoid bodies—clubbed and segmented forms, except small and ill-defined ones, being conspicuous only by their absence. The xerosis bacillus, be it noted, shows but a very scanty growth on alkaline potato, and even this scanty growth soon dies out.⁷

The recent observations of Abbott and Gildersleeve¹ on the occasional branching of the *B. diphtheriæ* as distinguished from the non-pathogenic members of the group, led us to hope that some assistance might be gained by studying the morphology of the bacilli we had isolated when cultivated for eight hours at 37° C. upon acid (+ 30) egg medium. In this hope, however, we were disappointed, as we were unable to obtain branched forms in any of the cultivations—not even in our control cultures prepared with virulent strains of *B. diphtheriæ*.

Finally, in some cases in which we failed to detect a diphtheroid bacillus, one and often more fresh swabbings were made and examined as thoroughly as in the first instance.

(b) *Material obtained Post Mortem*.—At the *post-mortem* inspection of the bodies of general paralytics, some, and often all, the material detailed below was collected for examination, and generally in the order there given. The methods of examining the cultures prepared from this material corresponded exactly with those already described. In the event of a culture failing to develop a growth, the period of observation was extended from eighteen hours to seven days before recording the result as sterile.

(1) *Cerebro-spinal Fluid*.—The skin of the dorsum over the lumbar vertebræ was seared with a red-hot cautery iron, and as much cerebro-spinal fluid as possible (up to 5 cubic centimetres) was drawn off by means of "lumbar puncture" into a sterile syringe. The syringe was then detached from the needle and the cerebro-spinal fluid transferred to a sterile test tube. The fluid was first reinforced by incubating at 37° C. for twelve to eighteen hours, then thoroughly centrifugalised, and cultivations prepared upon inspissated blood serum, nutrient agar, and in broth from the centrifugalised deposit, after a preliminary microscopical examination.

(2) *Swabbings from the Pharynx*.—These were obtained and examined in a manner precisely identical with the swabbings collected from the fauces during life.

(3) *Heart Blood*.—As soon as the thorax was opened an incision was made in the pericardium and the surface of the right ventricle, or occasionally the right auricle laid bare. This surface was then seared with the cautery iron, and the point of a sterile Pasteur pipette thrust through the seared area into the heart cavity, and a small quantity of blood (2 to 3 cubic centimetres) aspirated into the pipette. From the blood so collected cultivations were established in broth, and on agar, and inspissated blood serum.

(4) *Swabbings from Bronchi*.—The lungs were removed from the body and separated from the heart. A section across one or other lung, often both, was then made at a convenient spot, and a swab, such as was employed in the collection of material from the throat, was passed into

an open bronchus (avoiding contact with the cut surface of the lung) and pushed onwards, gently rotating it meanwhile, as far as it would go. It was then carefully withdrawn, returned to its sterile tube, and the latter labelled. The further steps of the examination were precisely as described for material from the throat and pharynx.

(5) *Bile*.—When the abdominal cavity was opened the gall bladder was sought for and drawn forward from under the edge of the liver. The exposed surface of the bladder was seared with the cautery iron, the point of a sterile Pasteur pipette thrust into the bladder through the seared area, and a few cubic centimetres of bile aspirated into the pipette. After collection, the examination of the material was proceeded with as described under heart blood.

(6) *Scrapings from the Mucous Membrane of the Intestine*.—The apparatus used for collecting the material consisted of a small tin scoop mounted in an ordinary cork. This cork was used to close the mouth of a test tube in such a manner that the scoop was enclosed in the tube. The whole piece of apparatus was then prepared for use by sterilising in the hot-air oven for half an hour at 150° C.

The cæcum was found and drawn forward, the peritoneal surface of the intestine just above the cæcum seared with the cautery iron, and an incision made through the walls of the intestine within the seared area by means of a sterile knife. The cork, with its attached scoop, was removed from a test tube, the scoop passed into the cavity of the bowel through the incision in the intestinal wall, and the mucous membrane thoroughly scraped. The scoop was then removed, and, with the material scraped from the bowel in its bowl, replaced in the tube. Scrapings from other portions of the intestinal canal were made in a similar manner.

Cultivations were established directly from the scrapings upon inspissated blood serum and agar, by means of a platinum loop.

*Results Obtained from Examinations of the Throat
during Life.*

The number of cases examined totalled up to 138, and comprised 60 cases of general paralysis of the insane and 78 cases of other forms of insanity. Of these cases, Colney Hatch Asylum provided 88, 49 general paralysis and 39 other forms of insanity; and Claybury Asylum 50 cases, made up of 11 cases of general paralysis and 39 other forms of insanity, as shown in Table II. :—

TABLE II.
SOURCE AND CONDITION OF THE PATIENTS EXAMINED.

Asylum	General paralysis of the insane	Other forms of insanity	Total all forms of insanity
Colney Hatch ..	49	39	88
Claybury	11	39	50
Total ..	60	78	138

Of these 138 cases, 24 gave positive results—that is, we were able to detect the presence of a diphtheroid organism in 24 of this total, or 17·3 per cent. Unfortunately, owing to a variety of causes, we were able to isolate the organism from 15 only of these positive cases; in the remaining 9 cases the differential diagnosis between *B. diphtheriæ* and other members of the diphtheria group had to be based upon microscopical appearances alone. Even in these cases, however, we believe—for the reasons previously given—the margin of error to be extremely small. Assuming our results to be correct, we noted the presence of the *B. diphtheriæ* in 7 of these 24 positive cases, (or 5·07 per cent.), the “diphtheroids” present in the remaining 17 cases being *B. Hoffmanni* 14 times, *B. xerosis* twice, and an unnamed pigmented species once.

Tables III., IV., V., and VI. give the results we obtained dissected and tabulated to show :—

(1) The incidence of diphtheroid organisms in the throats of the insane.

(2) The incidence of *B. diphtheriæ* in the throats of the insane.

(3) The incidence of *B. Hoffmanni* in the throats of the insane.

(4) The incidence of diphtheroid organisms (excluding *B. diphtheriæ* and *B. Hoffmanni*) in the throats in the insane.

TABLE III.

SHOWING THE OCCURRENCE OF DIPHTHEROID ORGANISMS IN THE THROATS OF THE INSANE.

Source	Cases of G.P.I. examined	Diphtheroid organisms found	Percentage incidence	Cases of insanity other than general paralysis examined	Diphtheroid organisms found	Percentage incidence
Colney Hatch ..	49	9	18.3	39	9	23.0
Claybury ..	11	1	9.0	39	5	12.8
Total ..	60	10	16.6	78	14	17.9

TABLE IV.

SHOWING THE OCCURRENCE OF *B. diphtheriæ* IN THE THROATS OF THE INSANE.

Source	Cases of G.P.I. examined	<i>B. diphtheriæ</i> found	Percentage incidence	Cases of insanity other than general paralysis examined	<i>B. diphtheriæ</i> found	Percentage incidence
Colney Hatch ..	49	2	4.08	39	2	5.1
Claybury ..	11	1	9.00	39	2	5.1
Total ..	60	3	5.00	78	4	5.1

TABLE V.
SHOWING THE OCCURRENCE OF *B. Hoffmanni* IN THE THROATS
OF THE INSANE.

Source	Cases of G.P.I. examined	<i>B.</i> <i>Hoffmanni</i> found	Per- centage incidence	Cases of insanity other than general paralysis examined	<i>B.</i> <i>Hoffmanni</i> found	Per- centage incidence
Colney Hatch ..	49	5	10·2	39	6	15·3
Claybury ..	11	0	0	39	3	5·1
Total ..	60	5	8·3	78	9	11·5

TABLE VI.
SHOWING THE INCIDENCE OF DIPHTHEROIDS (EXCLUDING *B. diphtheria*
AND *B. Hoffmanni*) IN THE THROATS OF THE INSANE.

Source	Cases of G.P.I. examined	Diph- theroids found	Per- centage incidence	Cases of insanity other than general paralysis examined	Diphthe- roids found	Per- centage incidence
Colney Hatch ..	49	2	4·08	39	1	2·5
Claybury ..	11	0	—	39	0	—
Total ..	60	2	3·3	78	1	1·2

In Table VII. we have shown the particular patients, together with the mental condition of each, from whose throats we have isolated "diphtheroid" organisms, divided into two sections according to the asylum from which they were derived. The further particulars given refer to the differential diagnosis of the organisms, based on the result of the microscopical examination of methylene-blue stained specimens, and show also the result of the examination of Neisser stained preparations, the sign + indicating that polar granules, indistinguishable from those characteristic of the *B. diphtheria*, are present (see Neisser); the sign — indicating that polar granules are absent; whilst the sign ± indicates the presence of atypical granules.

TABLE VII.
SHOWING THE IDENTITY OF THE DIPHTHEROID ORGANISMS OBSERVED.

Asylum	Name	Mental condition	Methylene-blue preparation—diagnosis	Neisser preparation, positive or negative
Colney Hatch..	Abbott	—	<i>B. Hoffmanni</i> ..	+
" ..	Abrams	—	<i>B. diphtheriæ</i> ..	+
" ..	Baker	G.P.I. ..	<i>B. Hoffmanni</i> ..	—
" ..	Denny	" ..	" ..	+
" ..	Galgaard	" ..	<i>B. xerosis</i> ..	+
" ..	Haszell.. ..	—	<i>B. Hoffmanni</i> ..	±
" ..	Hollinghurst ..	—	" ..	—
" ..	Kirkby.. ..	—	" ..	—
" ..	Leahay.. ..	—	<i>B. xerosis</i> ..	±
" ..	Moore	—	<i>B. Hoffmanni</i> ..	—
" ..	Rummery	—	<i>B. diphtheriæ</i> ..	—
" ..	Smith	—	<i>B. Hoffmanni</i> ..	—
" ..	Solomons	G.P.I. ..	" ..	+
" ..	Steward	" ..	<i>B. diphtheriæ</i> *	+
" ..	Taylor	—	" ..	+
" ..	Vail	G.P.I. ..	<i>B. Hoffmanni</i> ..	—
" ..	Wright, R. ..	" ..	<i>B. diphtheriæ</i> ..	+
" ..	Wright, W. ..	" ..	<i>B. Hoffmanni</i> ..	—
Claybury ..	8	" ..	<i>B. diphtheriæ</i> ..	+
" ..	23	—	" ..	+
" ..	45	—	" ..	+
" ..	46	—	<i>B. Hoffmanni</i> ..	—
" ..	49	—	" ..	—
" ..	50	—	" ..	—

* This organism eventually proved not to be *B. diphtheriæ* (v. Tables X. and XI.).

Results Obtained from the Examination of Post-mortem Material.

The total number of cases examined *post mortem* in this connection amounted to 36. These were all derived from the London County Asylum at Colney Hatch, and comprised 10 cases of general paralysis of the insane and 26 cases of other forms of insanity. Of these, 4 of the cases of general paralysis yielded evidence of the presence of diphtheroid organisms in the respiratory tract, but only 1 showed evidence of any general, and that probably terminal, infection, or even *post-mortem* invasion, by *B. Hoffmanni*. This organism was quite typical in its cultural reactions, and was totally devoid of virulence or toxicity. Of the remaining

5 cases, 1 (W. W.) whose throat had been examined about a month before death with positive results failed to give any evidence *post mortem* of the presence of diphtheroid organisms within the body. Of the 25 cases of forms of insanity other than general paralysis, 4 gave evidence of the presence of diphtheroid organisms in the respiratory tract, none of general infection.

TABLE VIII.
SHOWING THE OCCURRENCE OF DIPHTHEROID ORGANISMS IN POST-MORTEM MATERIAL.

	Number of cases examined	Diphtheroid bacilli found in the respiratory tract	Percentage	Diphtheroid bacilli found in other situation as well	<i>B. diphtheria</i> found in any situation
General paralysis of the insane	10	4	40.0	1	0
Cases of insanity other than general paralysis of the insane	26	4	15.3	0	0

The full details of the *post-mortem* material examined from the ten cases of general paralysis, and the results obtained are shown in tabular form in Table IX.

In Tables X. and XI. are given the chief characters of the strains of diphtheroid bacilli which were isolated during the course of this investigation, contrasted with authentic stock cultivations of *B. diphtheria*, *B. Hoffmanni*, and *B. xerosis*. Finally, the pathogenicity of most of the diphtheroid bacilli we had isolated was tested in the following manner, premising that these and all the other animal experiments performed in connection with this investigation were carried out in the Bacteriological Laboratory of Guy's Hospital:—

Experiment 1.—One loopful (about 2 mg.) of a forty-eight-hour-old blood serum culture was emulsified in 1 c.cm. sterile broth and injected into the subcutaneous tissue of the abdomen of a small (250 gram.) guinea-pig.

TABLE IX.
RESULTS OF EXAMINATION OF *post-mortem* MATERIAL FROM GENERAL PARALYTICS.

Source	Name	DIPHTHEROID ORGANISMS NOTED			ORGANISMS ISOLATED FROM—				
		Swabbing of tonsils during life	Swabbing of pharynx	Swabbing of bronchus	Cerebro-spinal fluid	Heart blood	Bile	Scraping from intestinal mucosa	
1	C. B., October 30, 1903 ..	0	+	+	Sterile ..	(<i>B. coli</i>) ..	Sterile ..	—	
2	M. G., December 8, 1903 ..	0	+	—	" ..	Sterile ..	(<i>B. coli</i>) ..	—	
3	R. B., December 7, 1903 ..	+	0	—	(<i>Staphylococcus aureus</i>)	0	(<i>B. coli</i>) ..	—	
4	G. C., September 23, 1903	0	0	—	(<i>S. albus</i> and <i>aureus</i>)	0	Sterile	(1) Colon (2) Cæcum (3) Ileum	
5	J. F., November 9, 1903 ..	0	—	—	Sterile ..	(<i>B. coli</i>) ..	"	—	
6	E. H., January 25, 1904 ..	0	—	—	(<i>S. aureus</i>) ..	(<i>S. aureus</i>) ..	"	—	
7	R. L., January 18, 1904 ..	0	—	—	(<i>S. albus</i>) ..	Sterile ..	"	—	
8	J. S., November 23, 1903 ..	+	+	+	0	(<i>B. coli</i>) ..	(<i>B. coli</i>) ..	—	
9	G. H. V., October 6, 1903	+	+	+	<i>B. coli</i> ..	(<i>B. Hoffmanni</i>)	Sterile ..	(<i>B. Hoffmanni</i>)	
10	W. W., December 12, 1903	+	—	—	(<i>S. aureus</i>) ..	Sterile ..	0	—	

+ Indicates the isolation of a diphtheroid organism.

— Indicates a negative result so far as concerns diphtheroid organisms.

0 Signifies that this material was not examined.

TABLE X.—MORPHOLOGY AND STAINING REACTIONS OF DIPHTHEROID ORGANISMS ISOLATED.

Number	Name or Designation of bacillus	Source	Morphology on blood serum after 12-18 hours' incubation at 37° C. and stained carbolic methylene blue	"Gram" staining	"Neisser" staining	Branching on acid egg media at 8 hours	Morphology on alkaline potato after 24 hours at 37° C., and stained carbolic methylene blue	Diagnosis	Mental condition of patient
	<i>B. diphtheriae</i> (Powys)	Discharge from case of diphtheritic rhinitis	Straight or slightly curved rods, 2 μ or 3 μ —6 μ long by 0.5 μ —1 μ broad, ends rounded, frequently one or both slightly swollen; cell protoplasm aggregated into two, three, or more darkly-staining masses, sometimes showing meta-chromatism	+	—	Nil.	Large involution forms, showing marked clubbing and segmentation of protoplasm, and exhibiting metachromatism	<i>B. diphtheriae</i> ..	Sane.
	<i>B. diphtheriae</i> (Wood)	Discharge from ear in case of faucial diphtheria	Straight or very slightly curved rod, tapering to a fine point at either end; size as above; cell protoplasm aggregated into a lozenge-shaped mass in the centre and separated from the tapering sheath by a narrow unstained interval	+	+	"	Ditto	<i>B. diphtheriae</i> , var. sheath	"
	<i>B. Hoffmanni</i>	Laboratory stock. Originally isolated from discharge of post-diphtheritic rhinorrhoea	Short wedge-shaped cylindrical or oval bacillus, 0.8 μ —1.5 μ in length by 0.3 μ —0.5 μ broad. Ends both rounded or one rounded and the other tapering to a point. Parallel arrangement of individuals. Usually stains evenly	+	—	"	Short bacilli and coccoid bodies, some slightly pear-shaped. No clubbed or large barred forms	<i>B. Hoffmanni</i>	"
	<i>B. xerosis</i> ..	Laboratory stock. Originally isolated from normal conjunctival sac	As <i>B. diphtheriae</i> (Powys) above	+	+	"	As <i>B. Hoffmanni</i> , above	<i>B. xerosis</i>	"
1	Abbott ..	Swabbing from pharynx	As <i>B. Hoffmanni</i>	+	+	"	As <i>B. Hoffmanni</i> ..	<i>B. Hoffmanni</i> ..	—
2	Abrams ..	"	<i>B. diphtheriae</i>	+	+	"	<i>B. diphtheriae</i> ..	<i>B. diphtheriae</i> ..	—
3	Denny ..	"	<i>B. Hoffmanni</i>	+	+	"	<i>B. Hoffmanni</i> ..	<i>B. Hoffmanni</i> ..	G.P.I.
4	Galgaard ..	"	<i>B. xerosis</i>	+	+	"	"	<i>B. xerosis</i> ..	"
5	Hazell ..	"	<i>B. Hoffmanni</i>	+	+	"	"	<i>B. Hoffmanni</i> ..	"
6	Hollinghurst ..	"	<i>B. diphtheriae</i>	+	+	"	"	<i>B. Hoffmanni</i> ..	"
7	Leshay ..	"	<i>B. Hoffmanni</i>	+	+	"	"	<i>B. xerosis</i> ..	"
8	Rummery ..	"	<i>B. diphtheriae</i>	+	+	"	"	<i>B. Hoffmanni</i> ..	"
9	Steward ..	"	"	+	+	"	"	<i>B. diphtheriae</i> ..	"
10	Taylor ..	"	"	+	+	"	<i>B. diphtheriae</i> ..	<i>B. diphtheriae</i> ..	G.P.I.
11	Vail ..	"	"	+	+	"	<i>B. Hoffmanni</i> ..	"Diphtheroid 1"	"
12	Wright, R. ..	"	<i>B. Hoffmanni</i>	+	—	"	<i>B. Hoffmanni</i> ..	<i>B. diphtheriae</i> ..	G.P.I.
13	Wright, W. ..	"	<i>B. diphtheriae</i>	+	+	"	<i>B. Hoffmanni</i> ..	<i>B. Hoffmanni</i> ..	"
14	8 ..	"	<i>B. Hoffmanni</i>	+	+	"	<i>B. Hoffmanni</i> ..	<i>B. Hoffmanni</i> ..	"
15	50 ..	"	<i>B. diphtheriae</i>	+	+	"	<i>B. diphtheriae</i> ..	<i>B. diphtheriae</i> , var. "sheath"	"
			<i>B. Hoffmanni</i>	+	—	"	<i>B. Hoffmanni</i> ..	<i>B. Hoffmanni</i> ..	"

TABLE XI.—BIOLOGICAL CHARACTERS OF DIPHTHEROID ORGANISMS ISOLATED.

Number	Name or designation	Blood-serum culture at 24 hours	Agar streak culture at 24 hours	Gelatine streak culture at 3 days	Gelatine stab culture at 3 days	Alkaline potato	Glucose ferment broth culture. Anaerobic at 24 hours	Litmus milk culture at 3 days	0.5 per cent dextrose broth culture at 48 hours	Lead broth culture for presence of H ₂ S	Peptone water culture for presence of indol	Pigment formation	Nitrate broth for presence of nitrites
Controls	<i>B. diphteria</i> (Wood, Powys)	Small round pulvinate colonies, whitish or dirty-grey in colour, opaque, darker at centre, coarsely granular surface, entire margin	Generally as on blood serum, but translucent; or continuous dull whitish layer showing discrete colonies at the margins	As on agar but distinctly scantier growth	Line of small spherical colonies to bottom of needle track	Delicate, moist, glistening layer, so-called "invisible" growth	Flocculent or powdery growth deposited on sloping side of tube, or slipping to the bottom	+	+	+	+	Nil.	+
	<i>B. Hoffmanni</i>	"	"	"	"	"	"	+	0	+	+	—	+
	<i>B. xerosis</i> (subcultures)	As <i>B. diphteria</i> , but drier and scaly	"	Scanty growth as opalescent streak	Scanty growth	"	"	—	—	+	+	—	+
	Abbott ..	As <i>B. diphteria</i>	"	"	"	"	"	—	0	+	+	—	+
1	Abrams ..	"	"	"	"	"	"	—	0	+	+	—	+
2	Denny ..	"	"	"	"	"	"	—	0	+	+	—	+
3	Galgaard ..	"	"	"	"	"	"	—	0	+	+	—	+
4													
5	Haszall ..	"	"	"	"	"	"	0	+	+	+	—	+
6	Hollinghurst ..	"	"	"	"	"	"	—	+	+	+	—	+
7	Lehay ..	"	"	"	"	"	"	—	+	+	+	—	+
8	Rummery ..	"	"	"	"	"	"	—	+	+	+	—	+
9	Steward ..	As <i>B. diphteria</i> , but yellowish colonies	"	"	"	"	"	—	+	+	+	—	+
10	Taylor ..	As <i>B. diphteria</i>	"	"	"	"	"	0	+	+	+	—	+
11	Vail ..	"	"	"	"	"	"	—	0	+	+	—	+
12	Wright, R. ..	"	"	"	"	"	"	—	0	+	+	—	+
13	Wright, W. ..	"	"	"	"	"	"	—	0	+	+	—	+
14	8 ..	"	"	"	"	"	"	—	0	+	+	—	+
15	50 ..	"	"	"	"	"	"	—	0	+	+	—	+

+ = acid reaction, or presence of substance tested for. — = alkaline reaction, or absence of substance tested for.
 ± = faintly acid reaction, or traces of substance tested for. 0 = no change.

Experiment 2.—A similar dose was injected into a second guinea-pig and immediately followed by the introduction of 500 units of antidiphtheritic serum.

None of the guinea-pigs showed any ill-effects, either local or general, as the result of the inoculations.

Note.—Four of the animals used in these experiments died during the third week after inoculation, at which time peat moss litter was substituted for hay in their cages. *Post mortem* no evidence of infection by *B. diphtheria* could be detected. The intestines were enormously distended with macerated peat moss, and were ruptured in many places, the peat moss being found in the peritoneal cavity.

TABLE XII.
SHOWING RESULT OF INOCULATION OF BACILLARY EMULSIONS.

Guinea-pig No.	Weight in grams	Inoculated with "Diphtheroid" bacillus from	Dose of diphtheria antitoxin L.I.P.M.	Date of inoculation	Result
1	140	Abbott ..	Nil.	Dec. 10, 1903	Unaffected.
2	130	" ..	500 units	" "	" "
3	200	Abrams ..	Nil.	" "	Died Dec. 27, 1903.
4	200	" ..	500 units	" "	Unaffected.
5	200	Haszeli ..	Nil.	" "	" "
6	220	" ..	500 units	" "	" "
7	170	Hollinghurst ..	Nil.	" "	Died Dec. 29, 1903.
8	220	" ..	500 units	" "	Unaffected.
9	190	Leahay ..	Nil.	" "	" "
10	260	" ..	500 units	" "	" "
11	190	Rummery ..	Nil.	" "	" "
12	170	" ..	500 units	" "	" "
13	180	Taylor ..	Nil.	" "	" "
14	220	" ..	500 units	" "	" "
15	230	Steward ..	Nil.	" "	Died Dec. 27, 1903.
16	210	" ..	500 units	" "	" "
17	200	Wright, R. ..	Nil.	" "	" "
18	250	" ..	500 units	" "	" "
19	190	Wright, W. ..	Nil.	" "	" "
20	230	" ..	500 units	" "	Died Dec. 26, 1903.
21	150	Denny ..	Nil.	Dec. 11, 1903	Unaffected.
22	170	" ..	500 units	" "	" "
23	160	" 8 " ..	Nil.	Dec. 15, 1903	" "
24	150	" ..	500 units	" "	" "
<i>Controls.</i>					
25	180	Powys ..	Nil.	Dec. 10, 1903	Died Dec. 11, 1903.
26	220	" ..	500 units	" "	Unaffected.

Experiment 3.—Possible toxine production was tested by filtering a three-day-old broth culture through a porcelain candle, and injecting 5 c.cm. of the filtrate so obtained into a guinea-pig of about 200 grammes weight.

The animals so treated showed no symptoms whatever. Control animals inoculated under identical conditions with cultivations of true *B. diphtheriæ* (strains "Powys" and "Wood") and toxins obtained therefrom gave positive results.

TABLE XIII.
SHOWING RESULT OF INOCULATION OF FILTERED CULTURES.

Guinea-pig No.	Weight in grams	Inoculated with filtered cultures (? toxins) of diphtheroid bacilli from	Date of inoculation	Result
27	260	Abbott	Dec. 19, 1903	Unaffected.
28	210	Abrams	" "	"
29	190	Denny	" "	"
30	200	Hollinghurst ..	" "	"
31	160	Leahay	" "	"
32	270	Steward	" "	"
33	210	Wright, W. ..	" "	"
34	200	Wright, R. ..	Jan. 10, 1904	"
35	190	Haszell	" "	"
36	220	Taylor	" "	"
<i>Controls.</i>				
37	220	Powys	" "	Died Jan. 12, 1904.
38	200	Wood	" "	" "

Bearing in mind the possibility that the organisms isolated from the throats of the insane might be *B. diphtheriæ* of extremely low virulence, a further set of inoculations was carried out—employing for the purpose five strains of bacilli, diagnosed microscopically as true Klebs-Loeffler bacilli, two of *B. Hoffmanni*, and one of *B. xerosis* as follows:—

Experiment 4.—Three cubic centimetres of a forty-eight hour-old broth cultivation was injected subcutaneously into the abdominal parietes of a guinea-pig of about 250 grammes weight.

Control animals were inoculated with 1 cubic centimetre of similar cultivations derived from strains "Powys" and "Wood" respectively (Table XIV.).

The result of this experiment was that the animals inoculated with cultures from "Abrams" and "8" died at seventy-two and forty-eight hours respectively, the necropsies affording typical pictures of the death from infection by *B. diphtheriæ*. None of the other animals were affected.

The two control animals died within twenty-four hours.

TABLE XIV.
SHOWING EFFECT OF INOCULATING LARGE DOSES OF LIVING CULTIVATIONS.

Guinea-pig No.	Weight in grams	Inoculated with diphtheroid bacilli from	Organism diagnosed as	Dose of cultivation	Date of inoculation	Result
				c.cm.		
39	300	Abbott ..	<i>B. Hoffmanni</i>	3	Jan. 12, 1904	Unaffected.
40	230	Abrams ..	<i>B. diphtheriæ</i>	3	" "	Died Jan. 15, 1904.
41	270	Haszell ..	<i>B. Hoffmanni</i>	3	" "	Unaffected.
42	270	Leahay ..	<i>B. xerosis</i> ..	3	" "	"
43	240	Wright, R.	<i>B. diphtheriæ</i>	3	" "	"
44	270	Rummery	"	3	" "	"
45	290	Taylor ..	"	3	" "	"
46	300	"8" ..	"	3	" "	Died Jan. 14, 1904.
<i>Controls</i>						
47	260	Powys ..	"	1	" "	Died Jan. 13, 1904.
48	250	Wood ..	"	1	" "	" "

From these experiments it is clear that two of the strains of *B. diphtheriæ* isolated during our investigations were virulent, although the virulence, as indicated by the large dose required and the length of time that elapsed before death, was distinctly lowered, whilst the remaining three strains were, so far as we were able to judge, avirulent.

CONCLUSIONS.

As the results of our observations we would formulate the following conclusions:—

(1) That the percentage incidence of all "diphtheroid" organisms in the throats of the insane (17·3 per cent.) is not in excess of that noted in the sane population (18·5 per cent.) outside the walls of an asylum.

(2) That the percentage incidence of genuine *B. diphtheriæ* (5·07 per cent.) in the throats of the insane is smaller

still (a large proportion of the diphtheroid organisms noted were common saprophytic members of the diphtheria group of bacilli), and compares well with 6.9 per cent. in the healthy sane.

(3) That there is no evidence to show that *B. diphtheriae* is more common in the throats of general paralytics (5 per cent.) than in the throats of cases of other forms of insanity (5.1 per cent.).

(4) That the number of general paralytics examined *post-mortem* is too small to enable any definite conclusions to be drawn therefrom. At the same time, it is a significant fact the *B. diphtheriae* was not isolated from any of these cases.

(5) That the majority of the strains of *B. diphtheriae* isolated from the throats of the insane are of low virulence and slight toxicity, and so compare in these respects with the types found occasionally in the throats of the healthy sane.

(6) That having due regard to the above conclusions, we are unable to trace any causal connection between *B. diphtheriae* and general paralysis of the insane.

BIBLIOGRAPHY.

- (1) ABBOTT AND GILDERSLEEVE. "On the Branching Occasionally Exhibited by *B. diphtheriae*," *Centralb. f. Bakt., &c.*, 1 Abt. Originale, Bd. xxxv., p. 273.
- (2) BEATON, CAIGER, AND PAKES. "The Value of Neisser's Stain in the Diagnosis of Diphtheria," *British Medical Journal*, 1901, ii., p. 758.
- (3) BERRY AND WASHBOURN. "Advantages of Bacteriological Diagnosis as Instanced by the History of an Outbreak of Diphtheria in a Large School," *Trans. Epidem. Soc.*, xix., 1899-1900, p. 117.
- (4) CORBETT. "Bacteriological Examinations for Diphtheria," *Journ. of Hygiene*, i., 1901, p. 235.
- (5) EYRE. "On the Diphtheria Group of Bacilli," *The Illustrated Annual of Microscopy*, 1898.
- (6) EYRE. "On the Presence of Members of the Diphtheria Group other than the Klebs-Loeffler Bacillus in Milk," *British Medical Journal*, 1900, ii., p. 426.
- (7) EYRE. "On the Xerosis Bacillus," *Trans. Path. Soc.*, xlvii., p. 334, and *Journ. of Pathology and Bacteriology*, iv., 1896, p. 54.
- (8) GOADBY, KENNETH. "Utility of Bacteriological Examinations in a Diphtheria Epidemic in a School," *Trans. Epidem. Soc.*, xix., 1899-1900, p. 87.
- (9) GORDON. *Supplement to the Medical Officer's Report to Local Government Board*, xxxiii. (1901-2), 1903, p. 418.
- (10) GORHAM. *Journal of Medical Research*, xvi., 1901, p. 201.

- (11) KOBER. *Revue des Maladies de l'Enfance*, July, 1900; *Zeitschr. f. Hygiene*, xxxi., 1899.
- (12) *Journ. of the Massachusetts Association of Boards of Health*, July, 1902.
- (13) MEADE BOLTON. *Medical and Surgical Reporter*, lxxiv., 1896, p. 799.
- (14) MÜLLER. *Jahrbuch für Kinderheilkunde*, Bd. xii., 1896.
- (15) PARKE AND BEEBE. *New York Medical Record*, xlv., 1894, p. 396.
- (16) PETERS. "Diphtheria and Pseudo-diphtheria Bacilli," *Trans. Path. Soc.*, xlvii., p. 345, and *Journ. of Pathology and Bacteriology*, iv., 1896, p. 181.
- (17) ROBERTSON, McRAE AND JEFFERY. "Bacteriological Investigation into the Pathology of General Paralysis of the Insane. Preliminary Note," *Review of Neurology and Psychiatry*, i., 1903, p. 225.
- (18) ROBERTSON AND SHENNAN. "Experimental Observation on the Pathogenic Action of an Organism Resembling Klebs-Loeffler Bacillus from Cases of General Paralysis of the Insane. Preliminary Note," *ibid.*, p. 227.
- (19) ROBERTSON, McRAE AND JEFFERY. "Bacteriological Investigations into the Pathology of General Paralysis of the Insane," *ibid.*, p. 305.
- (20) ROBERTSON, "Histological Evidence of the Presence of an Organism Resembling the Klebs-Loeffler Bacillus in Cases of General Paralysis of the Insane," *ibid.*, p. 470.

Note.—Since the above observations were completed, fresh interest has been aroused in connection with the pathology of general paralysis of the insane by the views expressed by Dr. Ford Robertson in his Morrison Lectures delivered before the Royal College of Physicians of Edinburgh in January, 1906; for in these lectures he attributes the possession of specific pathogenetic properties to his *B. paralyticans*, and regards this organism as the causal agent in the production of general paralysis. As the grounds upon which these claims are based appear to the critical observer open to question, further observations on the rôle played by members of the diphtheria group of bacilli in the production of general paralysis are now being carried out in conjunction with J. P. Candler, M.A., M.B., D.P.H., Assistant Pathologist at the Pathological Laboratories of the London County asylums, the results of which will be recorded in a future communication.—J. E.

BILATERAL LESION OF THE AUDITORY CORTICAL AREA: COMPLETE DEAFNESS AND APHASIA.

BY F. W. MOTT, M.D., F.R.S.

Case of cortical deafness, sensory aphasia, paralysis and anaesthesia of right leg, temporary paralysis of arm and lower part of right side of face and tongue, from embolic softening in three regions of the brain supplied by posterior branches of the middle cerebral on the two sides and the anterior cerebral on the left side only. Softening and atrophy of the following regions of the cortex found post-mortem. The posterior third of the first temporal convolution, the greater part of the marginal, a portion of the base of the second temporal and a portion of the angular. In the left hemisphere the lesion was more extensive than in the right hemisphere, otherwise, the lesions were fairly symmetrical. This lesion would, undoubtedly, account for the cortical deafness and, presumably, for the aphasia. The hemiplegia with permanent paralysis and anaesthesia of the right leg was accounted for by a destruction of the whole of the mesial cortical surface of the left hemisphere which lies above the corpus callosum.

E. M. H., admitted to Claybury, March 18, 1897, aged 25; age at first attack 22, married.

Certificate.—She is very depressed, melancholic and emotional, frequently cries, and laughs and cries without any cause whatever; she is quite incoherent and unfit to take care of herself. Her husband states that she attempted to cut her throat on Friday morning the 12th inst.; she attempted to set the place on fire twice the previous evening, and threw a knife at the nurse. She is very violent, and imagines that he cohabits with immoral women.

Family History (from husband).—Sister and brother were hysterical. Father was a drunkard and lived a fast life, died at the age of 48. Brother died at the age of 29 or 30 from hysterical paralysis, was under treatment at St. Bartholomew's Hospital for a time; left a son who is strange and weakly, curious head (hydro-cephalic?) Married, July, 1894. Remained in good health mentally and bodily until first miscarriage, February, 1895

(about six months foetus), in Beckenham Cottage Hospital, under Dr. Sturgess. Second miscarriage November 17, 1895, while under treatment at Barming Heath Asylum.

Condition after first miscarriage.—Lost her hearing suddenly; three or four days later suddenly developed paralysis in right leg and arm, had convulsions and lapsed into unconsciousness. Was a patient at the National Hospital, Queen Square, under Dr. Beevor, May, 1895 (*vide notes*). After being discharged from Queen Square she continued to improve, was able to do all her usual housework, and could walk a distance of a mile or more comfortably. In October, 1895, she had a convulsive fit and a condition identical with the first attack was established, and she was sent to Barming Heath Asylum. Was at Barming Heath Asylum from October 28, 1895, to February 29, 1896 (*vide notes*). Very quiet, steady and modest. No reason to believe her otherwise before marriage. When discharged from Barming Heath in February, 1896, she was in the same physical state as on admission to this asylum. Mentally, she was cheerful, happy and comfortable. This continued up to three months ago when she began to fret, lost her appetite and became exceedingly irritable. She gradually became worse; see husband's statement in certificate.

Physical condition on admission.—Fairly nourished. Tongue clean, protruded in middle line, no facial paresis. No apparent anæsthesia or hyperæsthesia. Palate wide. Teeth good. Appetite good. Bowels constipated. Catamenia: serum in breasts. Pulse very fair, 88. Sight impaired. Pupils: optic discs normal, some fixation of outer half of left iris; no nystagmus. Spastic paralysis of right leg. Intention tremor in left arm, wasting of muscles of right leg. Ankle clonus both sides.

Mental condition.—She is very emotional. She can only articulate one or two words and those very indistinctly. She is irritable and at times depressed. She is deaf to ordinary vocalisation, neither does she give any indication of hearing a tuning-fork applied to her head. She understands anything of a simple character when written, though she appears to puzzle over it for some time. She has aphasia and can only partially express herself in writing.

ADDITIONAL NOTES.

Letter from Practitioner.

28, St. Paul's Road, Canonbury.

March 30, 1897.

DEAR SIR,—I cannot remember the year I first saw the above, but I can the principal features of the case. When called to her she presented the ordinary symptoms of a hemiplegia with aphasia, but as I could not find any cause for the condition, I put it down

to hysteria, and I think the subsequent course proved I was correct. If I remember rightly she had complete hemianæsthesia. The paralytic symptoms disappeared rapidly, but the aphasia remained complete for a week or more, and partial for something like a month. She completely recovered under tonics and valerian. I then lost sight of her, but after her marriage she came up to stay with her mother-in-law and they called me in to see her. I found her with some apparent spastic gait, complete deafness and aphasia, and during all my attendance we never actually got her to speak, or to acknowledge that she heard. The mother-in-law was a very cute person and she informed me that several times when not observed, the patient appeared to understand what was going on and would turn her head when anyone entered the room suddenly. She was subject to violent outbursts of passion and would utter noises, but never spoke. Her knee-jerks were greatly exaggerated but I do not remember whether she had any anæsthesia or other sensory disturbances. She did not improve at all and left to go home to her husband. She was under treatment at Beckenham for some time, and, I believe, was in the Cottage Hospital.

CYRIL G. MACK.

NOTES FROM NATIONAL HOSPITAL, QUEEN SQUARE.

E. H.—In November, 1894, had a fright, followed by some family differences; seemed unnaturally worried. A fortnight later was vacant and absent-minded and stupid in the evening. Next morning, at 7 a.m., her husband found her quite helpless, had passed her water in the bed, could not understand what was said to her, but nodded appropriately in answer to written questions. During the day had another (hysterical?) fit, cried violently, but had no definite convulsions, but her husband noticed the bed shaking violently.

She was admitted to Beckenham Cottage Hospital completely paralysed on right side. After about a month began to recover her speech. The arm recovered rather rapidly and completely. On coming home the husband noticed she could not feel a prick or a pinch on the right leg (which was œdematous) but she could on the arm. She was able to read throughout her illness. Her leg has rapidly recovered power; complains of pains in right shin. Memory unaffected, no alteration in disposition. Said not to be emotional.

Personal History.—Married in July, 1894. Had premature birth two months after onset of hemiplegia.

Family History.—No history of paralysis. One brother died of fright, aged 27; said not to be insane.

In 1893 patient had a similar attack after a fright, supposed ghost;

was UNCONSCIOUS FOR THREE HOURS, LOST HER SPEECH FOR TWO WEEKS, BUT THERE WAS NO PARALYSIS AND SHE RAPIDLY RECOVERED.

On admission, May, 1895. Right leg weak. Can only say yes and no; understands all written commands; cannot write spontaneously. Apparently has attacks of giddiness. Nystagmus. Jaw deviates to R. Left side of mouth acts better than right. Deaf. Slight anaesthesia in right leg. Left knee-jerk more than right.

Notes of an examination shortly after admission to Claybury Asylum by myself.—She is quite unable to comprehend a single word spoken to her, and is apparently stone deaf. I was unable to convince myself of this, although it is probable, for a tuning fork applied to the skull on both sides did not attract the slightest attention; but she was then absorbed in watching her observers, therefore it may have been due to inattention. The patient can understand written or printed language, and this is the only means of communicating with her. She appears to understand simple sentences, *e.g.*, question I. "How long have you been married?" was written down, then 1, 2, 3, 4, 5 years underneath; she expressed by gesture and sounds dissatisfaction; then 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 months was written down, she still expressed dissatisfaction; finally two years and 1, 2, 3, 4, 5, 6 months was written down; as soon as six was reached she became very pleased and excited and spontaneously said "is that." The time was nearly correct.

Question II. "How many children have you had?" and the numerals 0, 1, 2, 3, 4 were written down, at which again she showed signs of dissatisfaction. I then wrote miscarriages 2, at which she became very excited, and said "is that." She makes exaggerated attempts by vocal sounds to express simple emotions of pleasure or disgust, the former being much higher in pitch, *ee* equals pleasure with elevation of the head; *ah* uttered very gutturally associated with a lateral movement of the head downwards was an expression of displeasure. She was therefore able to understand the meaning of simple sentences and to exercise reason. There is only partial word-blindness, this manifesting itself by evidence of confusion, and signs of inability

to understand the meaning of a sentence when fatigue has been produced by repeated experiments.

Writing from copy.—She can write, but to a very limited extent, *e.g.*, she copied the word *pencil*, she copied her own name, but when asked to copy *chair* she tried to write “now copy this chair,” showing that she did not understand this simple sentence and the logical sequence it bore to the previous sentence.

Spontaneous writing.—When requested by writing to write her age, she wrote down the numbers 2, 1, 1, 1, 1, 1, as if she were unable to recall the figure 5; asked to write her address and name, she began with a correct H but was unable to proceed further. At another time she was able to write four letters of her surname correctly. She attempted to write her address, beginning with the correct letter, but became more confused as she proceeded, until the writing was quite incoherent; the same was observed when asked to write her husband’s name. She recognises all ordinary common objects by sight, and shows signs of satisfaction when the right name is written to designate the object, but she soon tires and gets confused when asked to select one from several objects. Not only is all spontaneous speech lost, but she is quite unable to repeat aloud what she has written, to count, to say the alphabet, or to repeat her own name, although once or twice she will get out the first letter or syllable of a word.

Taste and smell were tested and it was concluded that she possessed these senses; when ammonia was placed near her nostrils, and at the same time the written question, do you smell this? shown to her, she became very emotional and said “is that.” There is some paresis of the lower part of the right side of the face. The grasp was good in both hands, wrist-tap and triceps jerk obtained both sides. She had apparently no loss of sensibility; when pricked or touched she showed signs of feeling on both sides. The right paralysed leg was especially tested and no defect was ascertained. The heart sounds appeared normal, there was no thrill. It was further noticed that when she used her right hand in writing she apparently had some difficulty

in judgment of distance, as if there were lack of association of the hand and the eye in this coördinate movement. There was noticeable tremor in the left hand of a coarse character, which was not however increased in amplitude during effort. She was discharged from the asylum suffering from organic disease of the brain and admitted to Colney Hatch Asylum, June, 1898. The following notes were made:—

Heart: first sound somewhat altered, being somewhat muffled and at times reduplicated. No murmur to be heard. Respiratory and abdominal organs healthy.

Mental Condition.—It is difficult to ascertain the patient's mental condition, as she is aphasic. She is word-deaf, being unable to understand spoken language. She is unable to express herself in spoken language, is able to understand written speech, but is unable to express herself in writing. She can point out objects correctly, and can also point out her age when shown figures. When she attempts to answer a question she becomes excited, makes inarticulate noises and laughs childishly. She is able to look after herself, such as taking her food, washing, dressing her hair, but is unable to walk on account of paralysis of her right leg, which she can only move to a slight extent voluntarily.

September, 1898.—I found her in much the same state as she was when at Claybury, twelve months previously. She recognised me immediately although she had not seen me for twelve months, and expressed great satisfaction. The following note was made by Dr. Cole on June 30, 1899. Absolutely aphasic and also word-deaf; vision considerably impaired, but she recognises persons fairly easily; can recognise some words, as cat, dog, pig, &c., if written in capitals; she accurately associates the names with pictures of these animals, correcting, sorting out, or selecting for each its proper name. Simple sentences she could not be made to understand. (There is, therefore, a difference in her condition to that exhibited when in Claybury a year before.) Such a sentence as "Does your head ache?" was tried without result. In attempting to read she screws and rubs her eyes, and varies the distance of the paper from the eyes, indicating either some visual defect or an inability to understand why she cannot grasp the meaning of the symbols. Her power of attention and concentration seems impaired; by her expression of face and the way in which she rubs her forehead, she seems to have sudden sharp pains in the head. Dr. Cole thus interpreted this: more probably it was an attempt by gesture to show her defect of speech through the brain disease, for the next moment she would be laughing. The

notes state that she rubs her right thigh occasionally as if painful; more probably again, this is to show that the paralysis of this limb prevented her walking. She cannot walk unsupported, but is wheeled about the grounds in a chair. There is no squint, no facial weakness; the pupils are of moderate size, equal, react to light and accommodation. She is absolutely deaf and takes no heed of any sound, except, perhaps, the loudest noises, as for example, she apparently heard the fall of a curtain rail from near the ceiling. Frequently utters extraordinary sounds, and occasionally a few articulate syllables but these are never intelligible. There is marked rigidity of right leg in position of full extension and some rigidity of left leg. Both knee-jerks much exaggerated. Double ankle clonus, best marked on left side. Plantar extensor reflexes present. If made to walk, walks on tip-toe and crosses one foot over the other (scissors gait); but walking is painful to right leg. Some rigidity of right arm (only voluntarily), no rigidity of left arm. Hand grasps good. Coördination of right hand good. Coarse intention tremor of left arm resembling that of disseminated sclerosis; steady with right hand but spills with left. Supinator longus and triceps jerk present. There seems to be no defect of cutaneous sensation and none to pin pricks. No deformity of spine. Muscular development good. Often calls the attention of the nurses by crying out and pointing, if she sees other patients doing what they should not. *Her habits are clean.* Menstruation continues, but is somewhat infrequent. As to her mental state there is apparently some dementia, but it is difficult to determine its degree. General bodily health good.

I visited Colney Hatch Asylum, December 16, 1901, and made the following notes:—She recognised me when I entered the ward. When at Claybury she could write a few letters; she is now unable to do so. She can read simple sentences, and apparently understands the meaning. Thus: “Are you in Claybury? Yes or no?” Pointed to “no.” “Are you in Colney Hatch? Yes or No?” Pointed to “yes.” “Which is Dr. Jones?” There were three doctors present and she recognised correctly Dr. Jones. “Put your tongue out.” Protrudes tongue slightly, deviating to the right. There appears to be a slight paresis of lower part of face on right side. She can imitate, showing her teeth and putting up two or more fingers. “Do you think you could use a typewriter? Yes or no?” Pointed to “no.” “Do you hear a noise? Yes or no?” She now became emotional and was apparently upset. A watch was placed

on the side of her head and shown to her. She shook her head indicating that she did not hear it.

Physical Examination.—No heart murmur detected. Walks with great difficulty—crossed leg progression. Spastic condition of both legs more marked in right. Foot drop, marked rigidity, exaggerated reflexes and ankle clonus on both sides. Coarse tremor of left hand, none in right hand. She feels the prick of a pin or a hot spoon in both legs, but response is somewhat delayed. There is no loss



of control over sphincters. The appetite is good. There is no difficulty in *swallowing or masticating her food*; she is also able to cut up her food. The attendant informs me that she gives no trouble, and that the menses are regular. She recognises her friends immediately, and often by sounds she will indicate to the attendants that other patients are getting into mischief.

April 7, 1902.—Signs of phthisis pulmonalis detected.

June 3, 1902.—Death.

Post-mortem Notes, June 6, 1902.

The body is emaciated. *Post-mortem* staining on dependent parts. Small bed sore on sacrum, and upon right great trochanter, and an eschar on right heel.

Skull.—Calvarium normal thickness. Over the upper and posterior part of right parietal region on the inner surface of the dura mater is a thin rusty-coloured false membrane the size of a crown-piece, otherwise the dura is normal.

There is considerable excess of sub-dural and sub-arachnoid fluid, which is quite clear. The veins of the pia mater are engorged. The brain substance is softer than natural, and there are three large areas of old softening in the following situations as seen in the photographs.

(1) Occupying the area of distribution of the anterior cerebral of the left hemisphere, and causing an atrophy of the middle portion of the mesial surface of the hemisphere involving the whole of the paracentral lobule in its mesial aspect, and the greater part of the gyrus fornicatus; in fact, the whole of the mesial surface above the corpus callosum. No doubt this lesion accounted for the paralysis and anæsthesia of the right leg (*vide* fig. 2). Following Dejerine this lesion corresponds to the area irrigated by the middle and posterior branches of the anterior frontal. Probably some of the branches entering the anterior perforated spot would be occluded.

(2) An area corresponding to the posterior third of the first temporal convolution, a large portion of the hinder extremity of the second, nearly all the supra-marginal except a small anterior limb. The supra-marginal and temporal annectant gyri of the angular gyrus. This was, no doubt, due to obstruction of the posterior division of the left middle cerebral (*vide* fig. 1).

(3) A similar but smaller area of softening in the right hemisphere, involving the posterior third of the first temporal, including the gyri of Heschl, the posterior part of the second temporal and its annectant with the angular, the posterior and inferior part of the supra-marginal and its

annectant with the angular (*vide* fig. 3). The right hemisphere, after stripping, weighed only 429 grammes, and the left hemisphere 328 grammes. As the convolutional pattern is complex and indicative of a good normal female brain

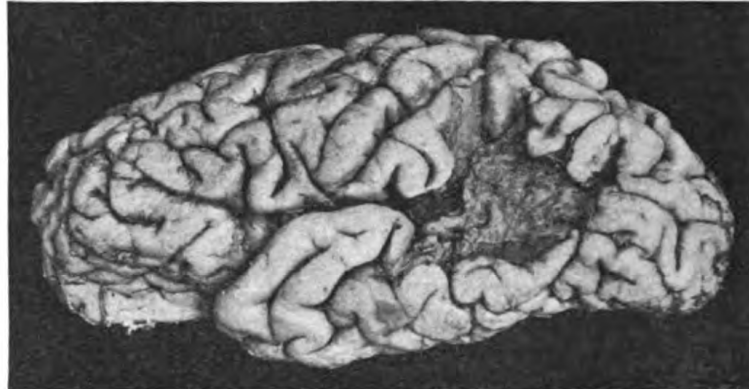


FIG. 1.—LEFT HEMISPHERE STRIPPED, SHOWING CORTICAL LESION. It will be observed that the whole hemisphere is shrunken from above downwards, and that the whole of the angular gyrus is not destroyed.



FIG. 2.—MESIAL SURFACE OF LEFT HEMISPHERE. It will be observed that the cortical area, irrigated by the anterior branch of the anterior frontal, is not affected.

before the lesions occurred, it follows that the loss of substance has been profound. The corpus callosum was observed to be very thin and wasted, and almost transparent in a region corresponding to the mesial softening. The splenium is the part least affected.

Thorax.—No effusion into pleural cavities, but adhesions at both apices. Both lungs riddled with tubercle with cavitation of the upper lobes, especially on the right side.

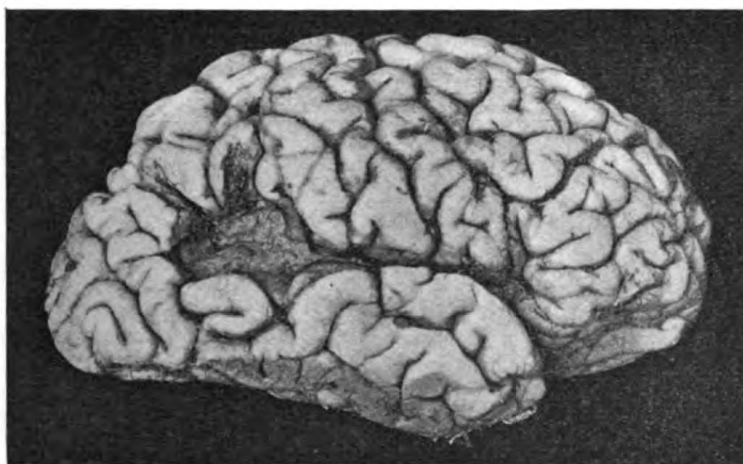


FIG. 3.—RIGHT HEMISPHERE STRIPPED. It will be observed that the lesion is mainly confined to the auditory cortical area.

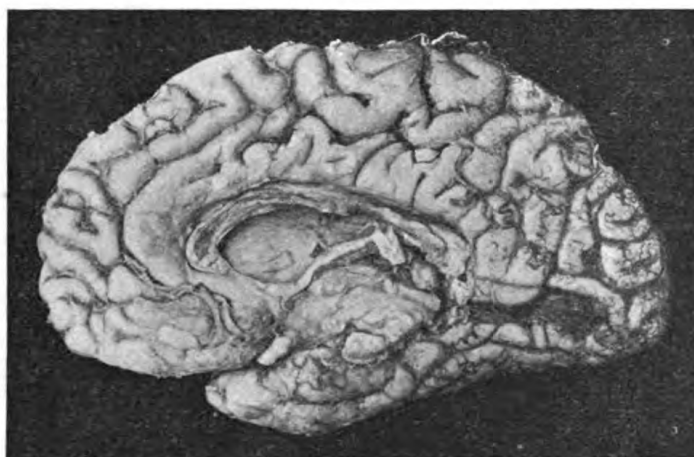


FIG. 4.—RIGHT HEMISPHERE STRIPPED, MESIAL SURFACE. The black patch on the mesial surface of the occipital lobe is not due to softening.

Right $28\frac{1}{2}$ oz., left $27\frac{1}{2}$ oz. Heart, $7\frac{1}{2}$ oz., contracted. Muscle firm, pale brown. Aortic valves competent. Mitral valve, old sclerotic vegetations on superior surface of orifice. No marked dilatation or signs of failure.

Liver 50 oz., congested, fatty. Kidneys, right $3\frac{3}{4}$ oz., left 3 oz., capsule adherent, cortex diminished, surface uneven, probably the result of old embolic process. Spleen 5 oz., two opaque thickenings of capsule, result of old infarcts.

Cause of Death.—Pulmonary tuberculosis.

F. W. M.

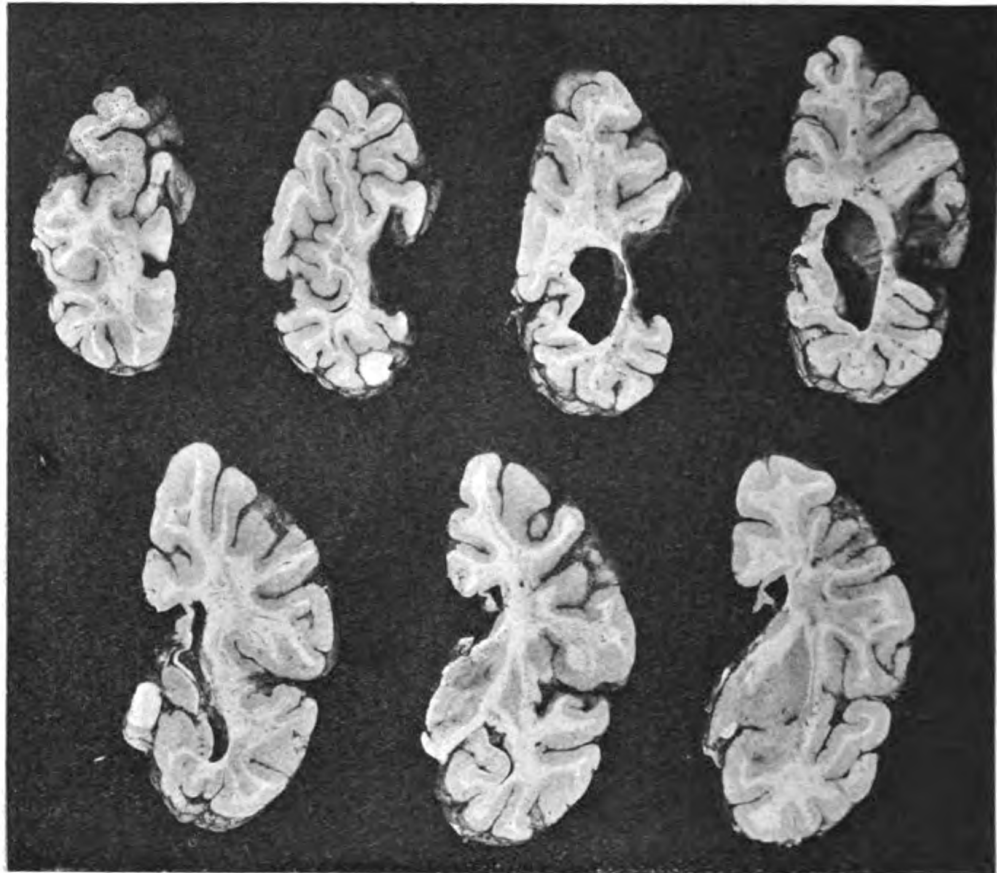


FIG. 5.—PHOTOGRAPH OF SECTIONS THROUGH THE RIGHT HEMISPHERE TO SHOW THE EXTENT AND DEPTH OF THE LESION. It will be observed that in the centre of the lesion there is only a very thin layer of white matter covering the lateral ventricle.

Commentary.—In all cases of embolic softening it is extremely difficult to decide how far the symptoms manifested during life are due to destruction of the grey matter of the cortex cerebri in particular localities, and how far to

recognisable and unrecognisable softening and destruction of the sub-cortical white matter; which consists not only of fibres proceeding to and from the area of cortical matter destroyed, but likewise of association systems uniting other and even remote apparently undamaged cortical areas. Where there have been a number of lesions produced by embolic occlusion, as in this case, it becomes extremely difficult to make any *positive assertions* in respect to correlation of function and destruction of definite cortical areas. With this reservation I will attempt, however, to correlate the lesions found *post-mortem* with the symptoms manifested during life. The patient's illness may be divided into three stages, one before marriage, and two after. At no time was the mitral stenosis, which caused the lesions, recognised by the existence of definite physical signs, although reduplication of the first sound was noted. The symptoms were at first considered to be hysterical.

The notes obtained from the friends at the National Hospital, corroborated by a letter from Dr. Mack, show that at 20 years of age, and before her marriage, the patient (after a fright by a supposed ghost) had an attack of loss of consciousness which lasted three hours; the speech was lost for two weeks and impaired for a month, but there was *no paralysis*, and she rapidly recovered. There is no mention of her being deaf; presumably she was, because the attack was similar. The practitioner regarded this attack as hysterical in nature, but the *loss of consciousness for three hours* and the statement of the friends combined with the *post-mortem* findings, allow of a completely different interpretation.

It is probable that an embolon lodged in the posterior division of the left middle cerebral beyond the origin of the ascending parietal branch, and caused softening of the left auditory cortical centre. This would produce word deafness and a temporary sensory aphasia without any paralysis; this rapidly cleared up, and she became a normal individual as regards her speech and mental condition, for she was married in July, 1894. In the following November she had a fright, followed by some family differences; a

fortnight later she had two fits. The first fit, according to the husband's statement, coincided with the development of *deafness* and *aphasia*, but ability to understand written questions. It may be considered that this was due to embolic occlusion of the posterior branch of the right middle cerebral artery. The deafness was now absolute and permanent; it may be accounted for by the complete *bilateral* destruction of the auditory cortical centres. The aphasia also was complete and permanent. The second attack, which occurred according to the husband, the same day on which he noticed *the bed shaking violently* was possibly associated with the blocking of the left anterior cerebral artery. These two attacks are difficult to separate, but it is probable that the shaking of the bed was the result of clonic spasms, indicating softening of the motor area of the leg.

After being in the Beckenham Cottage Hospital at the end of January, 1898, we hear of her next at Queen Square Hospital, and the notes of Dr. C. Beevor conclusively prove that she was aphasic and her condition as regards speech defects about the same as when I saw her at Claybury. Her physical condition subsequently deteriorated either from extension of thrombosis, first embolism in sub-cortical structures, or from contracture and disuse of the limbs.

I think it may be concluded that there was *absolute deafness*, and that this was due to destruction of the cortex on both sides corresponding to the region in which auditory sensory projection fibres terminate; viz., the posterior third of the first temporal, the transverse gyri of Heschl and the posterior part of the second temporal.

There certainly was not word-blindness and the optic memory images were present, for she could associate correct words with pictures; moreover, although she was unable to write, she was able to understand the meaning of simple sentences, even shortly before her death, although she easily became fatigued.

The evidence of facial paresis observed cannot be explained by the obvious cortical lesion and it was probably

due to subcortical damage caused by blocking of the anterior perforating arteries.

It is necessary to mention this, because M. Marie in an important paper contained in *La Semaine Medicale*, May 23, 1906, "La Revision de la Question de l'Aphasie," rightly points out that the area of cortex destroyed is not a true index of the damage to the brain, and by assigning functions to areas of cortical destruction without considering the possibility of the loss of function being due to destruction of sub-cortical fibres belonging to other regions we have fallen into a great error. Whether in his desire to call attention to this fallacy which undoubtedly so many people have fallen into, he has overstepped the mark in asserting that the third left frontal convolution does not play any special rôle in the function of language, and that the *sensorial aphasia of Wernicke* can no longer be accepted, subsequent careful observations will show. At any rate, a pronouncement by so distinguished a neurologist has come as an earthquake to our cherished beliefs in cerebral localisation; yet he is right in asking all observers to look to the facts and not follow preconceived ideas based upon a scheme. As he states very few cases are free from such fallacies if we consider them without prejudice.

Dejerine in the *Presse Medicale*, July, 1906, has criticised in a masterly manner the above destructive pronouncement of Marie in a paper entitled "L'Aphasie sensorielle et l'Aphasie motrice. Localisation et Physiologie pathologique."

M. Marie lays great stress on the loss of intelligence which lesions of the zone of language occasion, but M. Dejerine points out that a general paralytic can speak and write, but the dementia is much more pronounced than in an aphasic individual. I quite agree with him, and I think this case shows that disturbances of speech and disturbances of intelligence are processes of essentially different nature. M. Marie states, "si, pour ma part, j'avais á donner une definition de l'aphasie le fait que je m'efforcerais surtout de mettre en lumiere serait la diminution de l'intelligence."

If we look at the photograph of this patient, if we con-

sider her acts, her endeavours to make people understand her own wants, and her desire to help the attendants when the other patients were getting into mischief, also the fact that her habits were clean, that she recognised me after a year's interval, everything shows that she reasoned, and that the mental impairment although undoubtedly great, was more apparent than real. She comprehended her surroundings, and reasoned and acted to the best of her ability in response to the stimuli arriving in her cerebral cortex by the sensory avenues of intelligence still open. Considering the enormous amount of cerebral destruction as shown by the loss of brain weight, her mental condition compared most favourably with the average asylum patients, whose brains seldom lose anything approaching the amount of loss by this patient, which must have been quite one fourth of the total brain weight.

In 1874 Wernicke published his important memoir entitled "Der Aphasische Symptomencomplex," and in this paper he called attention to, and explained, word-deafness, and accurately determined the region at fault, viz., the posterior half of the first temporal convolution with perhaps a portion of the hinder extremity of the second. Word-deafness and word-blindness were, however, explained by Bastian as early as 1869, in a paper entitled "The Various Forms of Loss of Speech in Cerebral Disease."

Marie states, *loc. cit.*, p. 3: "Rien, absolument rien, au point de vue de la stricte observation clinique ne nous autorise actuellement à considérer la première circonvolution temporale comme étant le centre de l'audition et Wernicke a commis une erreur manifeste quand il a pris la notion de ce centre auditif pour en faire la clef de voûte de sa doctrine de l'aphasie sensorielle."

Bastian in his Lumleian lectures, "Some Problems in connection with Aphasia and other Speech Defects," *Lancet*, 1897, states that he only knows of four cases of double lesion of the superior temporal convolutions. The first case recorded was by Kahler and Pick, the second by Mills, third by Friedlander and Wernicke, and the fourth, a case of great importance, by Pick.

Defects resulting from destruction of the auditory and

visual word centres in each hemispheres. There is only one case on record in which these combined lesions have existed in the two hemispheres; it was published by J. C. Shaw in the *Archives of Medicine*, New York, the notes however were from the King's County Lunatic Asylum and are very meagre.

An extraordinary case has been recorded by Pick, which seems moreover quite incapable of being understood except by the supposition of the adequacy of the direct action of the visual word centre upon Broca's convolution even for the production of correct speech. A day labourer aged 24 was completely word deaf, and behaved like a deaf person taking no notice of ordinary sounds near him. It was observed that he only noticed loud calls, clapping or ringing of bells, and these not always readily. Yet if one shouted at him unexpectedly, he said angrily, "Don't shout at me!!" and he often said spontaneously, "I can hear quite well, but I don't understand, I can hear a fly flying past me." His power of recognising musical airs that he previously knew was quite lost. He spoke fluently and only occasionally hesitated about the right word. He named objects shown to him correctly, but he was unable to repeat words and phrases.

The case I have reported, in my opinion, supports Bastian's views that the primary revival of spoken words during thought takes place in the great majority of persons by a sub-conscious process in the auditory centre, for word-deafness can alone explain the loss of speech in the first attack, and instantly that the patient became absolutely deaf from the second lesion, she again became dumb and remained so. The sub-conscious revival of word images precedes the correlated revival of the complementary kinæsthetic images and these again successively incite the associated groups of neurons in the bulbar centres. It has been shown by many observers, commencing with Stricker, Galton, Ribot and others, that different persons think in different ways according to the predominance of the visualising, auditory, kinæsthetic (or 'motor) faculties; a large proportion of individuals are however indifferents. Stricker

by experiments upon himself, and Galton by his investigations, found also that a large proportion of Fellows of the Royal Society were of the motor type; the auditory type is the rarest. Bastian (Lumleian lectures) argues that Stricker, by concentrating his attention upon the genesis of his own thoughts, undoubtedly brought its expressive side into undue prominence. As Taine says, "Plus on imagine nettement et fortement une action, plus on est sur le point de la faire . . . quand l'image devient très lumineuse, elle se change en impulsion motrice." Neither Ballet, a follower of Stricker, nor Stricker himself are able, they admit, to recall voluntarily the kinæsthetic impressions associated with the act of writing words. These results are contradictory and support the views of Bastian, that the thought of a word revived in the auditory word centre naturally runs on to an incipient articulation, while on the other hand the mere thought of the word has no appreciable tendency to evoke writing movements. "Auditory and visual memories are the real linguistic counters for thought." This also appears to be Herbert Spencer's view (Principles of Psychology, vol. 1, p. 187), since he says: our intellectual operations are indeed mostly confined to the auditory feelings as integrated into ideas of objects, their relations, and their motions."

Bastian continues, "although the first stage in the revival of words seems to occur in the auditory centre, the molecular disturbance thus initiated is, however, immediately transmitted in a varying extent in two directions. It is transmitted to the visual word centre on the one side, and to the glosso-kinæsthetic on the other; to the latter strongly when the latter is to issue in speech, and to the former strongly when it is to issue in writing."

The patient was unable to revive in thought the words to enable her to write spontaneously, although she was able to copy a little. Neither her glosso-kinæsthetic nor her cheiro-kinæsthetic centres were affected, and the visual word centre was but partially affected, and these facts support the above dictum of Spencer. The woman was much more likely to have been an *indifferent* than an *auditive*, even if she were

a visual, and we may thus attempt to account for the partial retention of the visual memory of words even with such an extensive lesion of the visual word centre and subjacent cortex of the left hemisphere and a considerable destruction of the same sphere in the right.

The fact that she was unable spontaneously to initiate written speech, although her ability to read and to understand simple sentences (when I saw her) and to name correctly objects by means of printed or written letters and words, showed that her visual word centre was not entirely destroyed. This suggests to my mind the correctness of the hypothesis that the *primary* revival of the articulation of words in her case took place in the auditory centres, and I would agree with Bastian that in *motors, visuals, and indifferents*, the primary revival of words takes place in that portion of the brain in which (in a child) speech first develops. In the child, words are first learnt by hearing certain sounds associated with certain objects, and simple thoughts connected therewith are acquired before the child has the power of articulating them. He sees an object before he can name it; he must revive those auditory impressions which he had previously heard associated with it, otherwise how can we explain the fact that a child in full possession of speech even as late as the fifth, sixth, or seventh year, if he becomes deaf will certainly become dumb, unless he is trained by lip reading, that is, unless the primary incitation to articulate speech be transferred from the auditory to the visual word centres. The facts related in this case do not accord with the statement of Bernard that the motor centre of speech may become independent of the sensorial centre which had presided over its education.

"There are however, certain exceptional persons (visualists) who, as it were, read rather than hear their thoughts and in whom [as Ballet says] the visual images of words acquire such an importance that they alone constitute the medium of their internal speech."

The general rule however, is that auditory images constitute the most potent representations of words (even in the

common class of indifferents), whilst visual images form the most potent representations of ordinary external objects.

In exceptional cases it seems that the ordinary functional coupling of the auditory with the glosso-kinæsthetic centre and of the visual with the cheiro-kinæsthetic centre is not adhered to. Thus the deaf-mute has to rely upon signs and gestures, or lip language, and he thinks in the main with revived visual symbols; and it is from the organic seats of these that incitations pass to related parts of the glosso-kinæsthetic centre.

Again, in children who have been born blind, but have nevertheless ultimately learned to write, a direct association must have become established between the auditory and cheiro-kinæsthetic word centres. In the simplest process of thought we have no limitation of activity to any one area, but there are widespread processes of primary activity in all these speech centres and their associated tracts in both hemispheres—an activity which is not limited to concept or percept centres, but spreads to all parts of the cortex of both hemispheres. It is generally accepted that lesions of the glosso-kinæsthetic and cheiro-kinæsthetic centres (even when both are affected) do not produce failure to comprehend the meaning of words written or spoken, although the patients themselves are unable to speak or write.

Marie criticises thus the views so clearly expressed by Bastian : “Le malheur est, que la theorie psycho-physiologique du langage n’étant pas exacte, la doctrine de l’Aphasie s’est trouvé également erronée,” *loc. cit.*, p. 4.

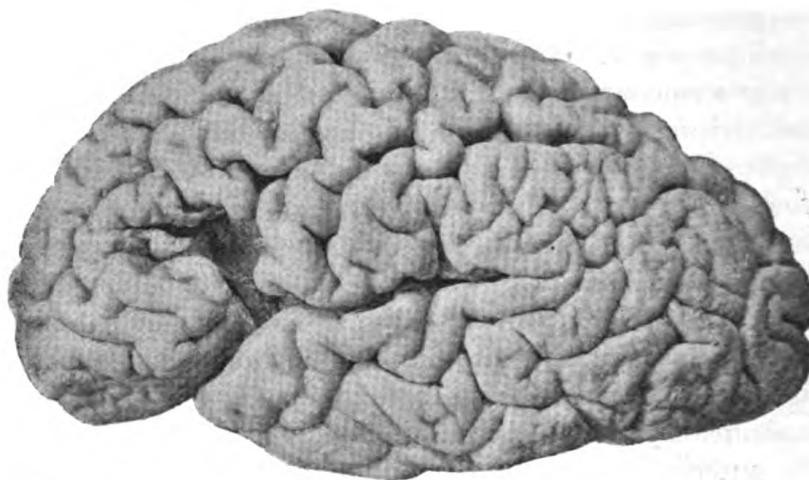
The degree of derangement from such lesions varies in different individuals, as one would expect, from relative potency inherited or acquired of the various centres. A more important and probable explanation is the variability of vascular supply and possibility of collateral circulation being established, and still more the escape or involvement of perforating arteries supplying sub-cortical structures.

Eight years ago a married woman of 30 came to my out-patient department with hemiparesis which soon passed

off, but left her with kinæsthetic aphasia and agraphia. She was unable to write either spontaneously or from copy, although she could apparently comprehend all that was written or said to her. It might be argued that she was unable to express herself by speech or writing, and therefore it was impossible to determine the extent of her powers of comprehension, but I made a very careful series of tests by showing her objects and then writing correct and wrong accounts of the same which were given to her to read; or a sentence was written down and she was told the nature of the written communication (sometimes correctly, sometimes not), and I judged by her gestures, occasionally accompanied by spontaneous yes or no, that her comprehension was not much impaired. She recently came to see me again, and I was surprised to find that she had regained her speech and writing. She told me somewhat slowly and with a slight effort, but with correct articulation, that it had very slowly returned, and it was years before she could frame sentences. For quite a year she was only able to say yes and no and a few other words. This woman suffered with mitral stenosis the same as the patient under discussion, and the fact that she was suddenly seized with transitory right hemiparesis with persistent aphasia and agraphia, I explained by an embolon having blocked the first branch of the anterior division of the middle cerebral artery, causing softening of Broca's convolution and the base of the second frontal. Most of the cases of affection of the speech kinæsthetic centres present aphasia, combined with agraphia, so much so that many authors, *e.g.*, Dejerine, denies the existence of a special writing centre, and he considers that any lesion of the zone of language affects all modes of speech, but that there is a predominance in the disturbance corresponding to the centre of images directly attacked by the lesion. Motor aphasia dominates if the lesion is seated in Broca's convolution; word deafness dominates if the lesion has destroyed the posterior part of the first temporal; word-blindness when the lesion involves the angular gyrus. Marie, however, denies the existence of an aphasia of Broca. There is only *one* aphasia, and the sole difference between

the aphasia of Wernicke and the aphasia of Broca is that in the former the patient speaks badly, in the latter he does not speak at all. According to Marie there must have been in this case a lesion involving the zone of Wernicke and a condition of anarthria due to lesion of the zone of the lenticular nucleus.

In connection with the foregoing I recall the following autopsy, which would have been of more interest if there had been any reliable notes. I made a *post mortem* on a woman who was admitted fifty years ago to Colney Hatch Asylum. She was designated an imbecile, but was a good worker in



This photograph is interesting in showing not only a destruction of Broca's convolution, but a low type of brain, frequently met with in asylums, in which there is a well-marked lunatic sulcus and calcarine fissure extending a considerable distance round the occipital pole. There is a deficient parietal development.

the laundry. After remaining at Colney Hatch a great number of years she was transferred to Leavesden where she remained twenty years, being there regarded as a harmless imbecile. She was sent back to Colney Hatch suffering with mania, and certainly was not speechless. No special notes at any time were taken regarding a speech defect. Doubtless, however, it was the speech defect in the first instance which led to her being termed an imbecile, for she was admitted long before Broca's discovery. The only infor-

mation obtainable from the notes was that her mental state was the result of disappointed love. At the autopsy I found evidence of very old mitral stenosis and an atrophic destruction of Broca's convolution (*vide* photo). Examination of the opposite hemisphere exhibited a secondary atrophy of Broca's convolution. In the absence of any reliable notes this is the interesting point of the case, for it suggests that corresponding cortical areas function together, although acquired habit may determine initial incitation in one hemisphere. This habit of initiating a function in one hemisphere (although both act) explains the reason why an adult loses speech when that area is destroyed in the left hemisphere, and either very slowly, or perhaps never, regains the function; whereas the same damage in childhood produces a much more temporary defect.

ALCOHOL AND INSANITY—THE EFFECTS OF
ALCOHOL ON THE BODY AND MIND AS
SHOWN BY ASYLUM AND HOSPITAL EXPERI-
ENCE IN THE WARDS AND POST-MORTEM
ROOM.¹

BY F. W. MOTT, M.D., F.R.S.,

*Pathologist to the London County Asylums; Director of the Patho-
logical Laboratory; and Physician to Charing Cross Hospital.*

So much has been written on this subject that I trust it will not be considered disrespectful to previous observers if I refer more particularly to my own experience and observations. As out-patient physician to Charing Cross Hospital, and latterly physician in charge of wards, I have had a considerable experience in seeing the effects of alcohol in the production of bodily diseases; but as Pathologist to the London County Asylums I have had a much larger experience in seeing the effects of alcohol in the production of mental diseases. I can safely say that in quite one fourth of the male cases which come under my observation at Charing Cross Hospital, and in a considerable proportion of the female cases, alcohol has been an efficient cause in the disease, or a very important co-efficient. In conjunction with venereal disease, especially syphilis, it is responsible for many degenerative processes, which will be alluded to. My house-physician, Mr. Reade, has kindly made a tabulated statement referring to the influence of alcohol in the medical cases admitted during the year 1905, which is appended.

The cases coming to Charing Cross Hospital of which intemperance has been the main cause of the disease are especially numerous on account of the situation of the

¹ An abstract of this paper was read at the Medico-Psychological Society, and published in the *Journal of Mental Science*, 1906.

hospital, and the class and the occupations of the patients who seek relief there. Located amidst the theatres, restaurants, music halls, and places of amusement and refreshment, it becomes the receiving-place for those who are intemperate in the pursuit of pleasure; also for a number of people engaged, either directly or indirectly, in the liquor traffic, or whose occupations lead to prolonged intemperance. Among such are potmen, barmen, barmaids, publicans, prostitutes, waiters, cooks and kitchen servants from hotels, stage carpenters, scene shifters, cabmen, 'bus drivers and conductors, and particularly numerous, the Covent Garden porters, who are addicted to drinking large quantities of beer. As a rule, all these people are, at the time they are brought to the hospital for such relief, in employment. I regard this as a very important point in connection with the nervous symptoms which may be manifested as a result of prolonged intemperance, because to the casual observer certainly, and to the skilled observer often, no mental deterioration may be discoverable in a large proportion of those chronic inebriates. Occasionally a head or other injury, slight or severe, the onset of disease, especially pneumonia or other infection, or an extra bout of drinking may result in delirium tremens, for which the patient may be brought to the hospital, or which may develop after he has been admitted and when alcohol is withheld.

A few cases proportionally of polyneuritic psychosis occur, especially in women, and the majority of these leave the hospital completely cured. All the mental symptoms pass off by withholding the alcohol and by careful diet and nursing, the paralysis caused by the neuritis persisting, as a rule, long after the mind has cleared. It is, however, difficult to judge whether the patient really is the same as before the onset of the mental symptoms.

This form of polyneuritic psychosis met with in hospital, occurring especially in women, but also in men, is identical with that met with in asylums, although not very common in either. It is far more frequently met with in women than men, in both asylums and hospitals, the proportion

being about one male to seven females. In hospitals it is the paralysis and the neuritic symptoms which obtrude themselves, whereas in asylums it is the mental symptoms. Very seldom in any case, however, are the mental symptoms completely absent if the patient be carefully examined in hospital cases. Conversely in asylums (in spite of the fact that the knee-jerks may be present or increased instead of absent) some evidence of neuritis is almost invariably present and may form an important causative factor in the production of hallucinations and delusions. Examples of these various types will be given, and it will be observed that often it is a mere chance whether a patient suffering with polyneuritic psychosis be treated in hospital or asylum (*vide cases*).

Many of these cases with characteristic mental symptoms arise in married women, who, without perhaps ever having been drunk and incapable, have acquired the habit of continuous secret tippling. I may here remark that grocers' licences have facilitated secret drinking to an enormous extent among women. They drink because they feel miserable and depressed. Sometimes they commence the habit after an illness. Usually according to my experience, it is married women who suffer with polyneuritic psychosis, and I have observed that it is so frequently associated with some other morbid factor—*e.g.*, septic infection from a miscarriage or abortion, gonorrhœa, endometritis, parametritis, salpingitis, syphilis, pneumonia, or tuberculosis—that it is difficult to assert in these cases how far the mental and the neuritic symptoms are partially due to such cause, and not solely to the direct effects of the alcohol on the nervous tissues.

In some cases a gastritis occurs, and the patient is unable to digest and assimilate food and takes only drink. I have found so often rotten teeth and pyorrhœa alveolaris that I am inclined to think that gastritis may become infective in nature and consequently microbial toxins may be absorbed and damage the tissues.

The mental symptoms, both in hospital and asylum cases, are especially liable to arise at the climacteric period.

Here alcohol may be merely a co-efficient, a small quantity only of drink being the exciting factor in a person in whom there is an inherent unstable mental condition, and the symptoms might have arisen if the patient had not taken any stimulant. Again, in people who are the subjects of arterio-sclerosis in later life, and renal change, of quiescent organic brain disease, especially syphilis, softening, and oncoming paralytic dementia, small quantities of alcohol become an important exciting factor. Again, alcohol, even in comparatively small quantities, may convert the potential lunatic into a raving maniac, and it is specially dangerous to the epileptic and feeble-minded, leading in the former to the production of motor and mental fits and making him irresponsible and anti-social and sometimes very dangerous to himself and others. There can be no doubt that drinking in pursuit of pleasure in the well-fed is far less liable to produce insanity than drinking in flight from despair and misery by the ill-fed, emotional, and neurasthenic or neuropathic individual.

The quantity of alcohol which is daily consumed by the pillars of society is quite sufficient to convert an epileptic or potential lunatic or certain feeble-minded individuals into criminals or certifiable lunatics. In support of this statement, based upon my own experience, I would cite that of the inspector of Inebriate Reformatories, Dr. Branthwaite.

REPORT FOR THE YEAR 1905, CONCERNING CERTIFIED INEBRIATE
REFORMATORIES ESTABLISHED UNDER THE INEBRIATES ACT,
1879-1900.

Dr. Branthwaite, p. 10, remarks : Upwards of sixty-two per cent. of the persons committed to Reformatories under the Act are found to be insane or defective in varying degree.

" I am satisfied that the majority of our insane inebriates have become alcoholic because of congenital defects or tendency to insanity, not insane as the result of alcoholism, and that the drunkenness which preceded alcoholic insanity was merely the herald—the only obvious sign—of incipient mental disorder. In relation to the final insanity, drunkenness in such cases is the intensifier perhaps, but not the cause of the disease."

Concerning the congenital defectives, which are divided into

two classes : (a) comprising degenerates, imbeciles and epileptics, and (b) moral and social defectives, he remarks :

" A marked intolerance to the action of alcohol is present in both refractory and quiet class of defectives ; very small quantities of drink, no more than is taken daily without apparent physiological effect by an ordinary individual, being sufficient to cause disorderly and violent behaviour. Our experience in this direction has led us to accept the view that intolerance to the exciting effect of small quantities of alcohol may be considered a fairly certain sign of impaired mental equilibrium."

He protests against the treatment of these persons by short sentences to prison, and it is right for me here to remark that my experience entirely coincides with this view. Often in the notes of cases of so-called recurrent mania I have found that the patient was sent to prison for several short terms, and it was then ascertained that he or she was insane or mentally deficient or epileptic and sent to an asylum, from which institution they are too often discharged, to be again readmitted, the readmissions generally being brought about by some anti-social act, the result of intemperance. All these cases help to swell both the statistics of cures and cases due to alcohol, whereas really they are degenerates or congenitally feeble-minded. They may be feeble minded because they lack moral sense and higher control, or they may be intellectually deficient, and therefore unable to earn an honest living. Often there is a combination of a lack of moral sense combined with intellectual deficiency, and not infrequently epilepsy in its major or minor form.

The following brief abstracts of the notes of a case I recently saw at Hanwell very well illustrates a class of case which is not uncommon in asylums.

E. J., properly C—s.—Criminal sent from Wandsworth prison. Mother an epileptic, father a heavy drinker. Was in a truant school until 16 years of age. He has always been very troublesome, and has been many times in prison. He is one of a family of degenerates and habitual criminals. He drinks heavily and has done no work for a number of years. Informant (sister) is herself feeble minded. The patient's symptoms of insanity are visual and auditory hallucinations.

STATISTICS PUBLISHED IN THE REPORTS OF THE LONDON COUNTY
ASYLUMS RELATING TO ALCOHOL AS A CAUSE OF INSANITY.

Alcoholic indulgence has always been considered one of the most important, if not the most important, cause of insanity, I therefore thought it would be of interest to ascertain the percentage of the total admissions to the various London County

Asylums of cases in which intemperance was regarded as a causative factor. I commenced with the published reports of the year 1893, when the Asylums came under the control of the London County Council. The only inference that can be drawn from these statistics is that the variability of percentages depends upon the personal equation. Take for example the year 1902, Hanwell is the highest with 25·6 per cent., and Claybury the lowest with 11·2 per cent. Now if all the other Asylums showed a similar low percentage to Claybury, we might believe a wave of temperance had swept over London. Then two years later, in 1904, we find in 29·3 per cent. of the admissions to Claybury alcohol is an assigned cause, but at Horton it is only 12·2 per cent., and the other asylums stand between these two extremes. If all the returns had shown this great rise of 11·2 per cent. to 29·3 per cent. in two years, it might be inferred that a great wave of intemperance had swept over London. I see, however, no means at present of making these statistics uniform, for no two people think alike, and the personal factors of different individuals come in to such a large extent in judging what constitutes intemperance, that even if in the future the greatest care be taken to make the data accurate, there will necessarily be some considerable divergence in the returns. These figures, however, tend to show the unreliability of collected statistics.

It would be interesting to ascertain what is the percentage of total abstainers admitted to the asylums. Without being able at present to produce any precise data I think the percentage would come out considerably larger than many people think. Of course it would be necessary to take adults only. In this connection it is interesting to note that Sullivan,¹ in his valuable work on Alcoholism, after analysing the causes of intemperance and its relation to insanity, concludes "that in this country the proportion of cases of certified insanity in which alcoholism is the essential cause of disease falls a good deal short of the 16 per cent. at which it is rated in the official statistics, and may possibly be something under 10 per cent." He refers to "the inquiry conducted by the American Committee of Fifty, which showed that insanity was attributed to drink in 24·22 per cent. of the patients observed, but that only a little over half that number (viz., 12·22 per cent.) were genuine alcoholics," and to a similar investigation carried out by the Massachusetts Labour Bureau, in which 20·86 per cent. of cases were supposed to be due to alcohol, but only 16·9 per cent. were excessive drinkers. It may perhaps be worth mentioning as an interesting illustration of the danger of *post hoc ergo propter hoc* reasoning in regard to pseudo-alcoholic cases,

¹ "Alcoholism: A Chapter in Social Pathology," by W. C. Sullivan, M.D., Medical Officer in H.M. Prison Service.

that in both these inquiries total abstinence was found to be much more frequent than intemperance as an antecedent of insanity."

TABLE SHOWING THE PERCENTAGE OF TOTAL ADMISSIONS TO THE VARIOUS LONDON COUNTY COUNCIL ASYLUMS OF CASES IN WHICH "INTEMPERANCE" WAS REGARDED AS A CAUSATIVE FACTOR.

Year	Hanwell	Colney Hatch	Banstead	Cane Hill	Claybury	Bexley	Manor	Horton
1893	18.4	11.8	5.3	11.0	—	Not opened	Not opened	Not opened
1894	18.1	16.5	13.5	16.6	9.5			
1895	18.5	11.5	13.5	16.2	17.6			
1896	14.0	14.3	13.8	15.0	20.6			
1897	15.4	13.0	16.9	17.1	22.6			
1898	20.7	10.9	20.7	18.6	27.5	Not opened	Not opened	Not opened
1899	10.4	12.2	17.9	19.1	17.8			
1900	15.8	18.8	17.0	14.1	12.9	23.8	8.7	—
1901	18.8	15.0	15.0	16.8	13.2	23.2	6.5	—
1902	25.6	12.8	17.8	20.0	11.2	15.4	15.7	—
1903	14.0	13.2	16.5	24.7	19.1	20.6	15.9	—
1904	17.4	17.8	17.4	22.2	29.3	24.2	21.8	12.2
1905	15.9	13.2	19.2	20.2	26.9	25.7	11.6	14.2
1906	19.6	14.4	15.7	18.2	28.8	27.6	14.0	17.0

One would, however, think from the statements which have been made by persons in high and responsible positions, and from statistics quoted by an intemperate zeal for temperance, that if there were no alcohol there would be no insanity. While yielding to no one in the desire to see temperate measures adopted for the control and regulation of the liquor traffic, the care and segregation of chronic inebriates, and the prevention of inebriety, I am of opinion that there is no proof that insanity would diminish to anything like the extent that is believed by some enthusiasts if alcohol were abolished. The President of the Local Government Board has recently pointed out that the drink bill is diminishing, yet the ratepayer knows that insanity is increasing. I am not sure, indeed, that if an island could be set aside for all those who were total abstainers, whether there would not eventuate still a high percentage of insanity there. I feel certain, however, that there would be less disease and *far less crime and pauperism* than in the general population of this country. Dr. Bevan Lewis,¹ of the West Riding Asylum, Wakefield,

¹ "Alcohol, Crime, and Insanity," *Journal of Mental Science*, 1906.

has shown by tabulated statistics that the admixture of a maritime with a mining and manufacturing class was fatal to the sobriety of the community; that, in fact, inland and *agricultural* communities were the least inebriate, but had the highest ratios of pauperism and insanity; that inland and maritime *mining* and *manufacturing* communities were the most inebriate, and had the lowest ratios of pauperism and insanity, while maritime *mining* and *manufacturing* communities, above all others, were the most intemperate, and revealed the lowest ratios of pauperism and insanity. A dissociation between alcoholism and insanity was thus indicated, whilst the latter was allied with pauperism, want, anxiety, and other moral factors. Dr. Sullivan, *loc. cit.*, by careful analysis and tables, shows conclusively that in the regional distribution of insanity it is difficult to trace any evidence of alcoholic influence such as might be expected if alcoholism really accounted for a sixth of the total number of cases. Thus Lancashire, Warwick and Cheshire, which rank very high in the scale of alcoholism, and the mining counties, where drunkenness is very rife, are alike in showing very low rates of insanity. He concludes that alcohol as the essential cause of *certified* insanity falls a good deal short of the 16 per cent. at which it is rated in the official statistics, and may possibly be something under 10 per cent.

These valuable observations of Dr. Bevan Lewis and Dr. Sullivan present points in similarity with the observations of Sir Hugh Beavor on tuberculosis, who showed that an industrial population often exhibited a lower death-rate from tuberculosis than the surrounding agricultural population. He attributed this, in a measure, to deficient nutrition on account of wage-earning capacity. There is another and still more important factor, and that is the poor mental and physical state of the agricultural population near to large industrial centres. The mentally and physically capable migrate to the large towns for higher wages, leaving the physically and mentally feeble and unfit behind. Dr. John Macpherson, Morison Lecture, 1904, showed that in Scotland generally the ratio of insanity to

population tended to be low in those communities with a rising population, and high in those with a falling population, confirmed by Dr. Easterbrook. It is a well-known fact that the feeble-minded are especially prone to tuberculosis, which is a fortunate circumstance, for it tends to rid the race of poor types. Imbeciles and idiots are often unfertile, which is another reason for the dying out of a degenerate stock, but a degenerate stock frequently contains feeble-minded in all grades, some of which will not die out, but propagate in considerable numbers, and it is probable that no class of the community produces insanity to such a degree as the feeble-minded. The progeny begotten of a feeble-minded mother by a drunken father, according to my experience, is much more likely to be born mentally defective or become insane in later life than when both parents are intemperate but neither of inherent mental deficiency.

It is my opinion a sound stock may degenerate from stress of town life, with all its attendant evils of overstimulation of nervous structures associated with a deficient nutrition engendered by an impoverished quality of blood and a diminished specific energy of cell-protoplasm. Alcohol is not the only stimulant: there are many other stimulating substances which are daily consumed by a large proportion of the population—the extractives of an excessive meat diet, tea and coffee; but these are of comparatively little harm as compared with alcohol, for the reason that while they may stimulate the nervous system, they have not the same devitalising action on the living blood and tissues. The prolonged abuse of alcohol lowers the defences of the body against microbial invasion (Metchnikoff has shown that alcohol produces a diminution of the phagocytes); and the poisonous effects of alcohol are the result partially of the alcohol entering the system, but also to toxins absorbed from the alimentary canal owing to the devitalising effect of the alcohol on the mucous membrane of the stomach and intestines, causing chronic catarrh, failure of the action of the digestive juices, and liability to microbial infective inflammation of the stomach, especially

if there exist rotten teeth and pyorrhœa alveolaris. When one important vital organ suffers, then the whole chemical processes of the human laboratory become deranged and the blood vitiated. It is a question whether cirrhosis of the liver is not due as much to the absorption of various microbial and other toxins as to the actual effect of the spirits absorbed.

Again, alcohol inflames the emotions and excites the sexual passions, and many a young person under its influence (perhaps for the first time) contracts venereal disease, and this fact is of great importance in the consideration of the effects of alcohol in relation to the infertility of intemperate women.

But alcohol is not only directly responsible for the spread of venereal infection; it is also responsible, in a large measure, for the ravages of the disease when acquired, by lowering the natural defences of the organism. It is a matter of common experience how intractable a severe syphilitic nervous affection becomes if the patient is an alcoholic subject.

All thinking people are agreed that *the abuse of alcohol* among civilised nations is directly or indirectly the most fruitful cause of overfull prisons, workhouses, infirmaries, hospitals and asylums. According to the President of the Local Government Board, drink and gambling in this country are the curse of the industrial classes. Mr. Rowntree stated, at the dinner of the Temperance League, given by Viscount Peel, that two months' wages of each year of the working man are consumed in liquor. Mr. Whittaker stated that only one in eight voters were total abstainers, and that it was necessary to enlist the sympathy of the great majority of people who were temperate in the use of alcoholic beverages. That leads up to the great question, Why do the great majority of intellectual, sensible, and moral people, men and women of as high civic worth as total abstainers, drink alcoholic beverages? Dr. Parkes, than whom no one was more competent to speak, remarked in connection with moderate use: "The strongest argument, however, is that it seems incredible that a large part of the human race should have fallen into an error so gigantic as

that of attributing great dietetic value to an agent which is of little use in small quantities and is hurtful in large." In my opinion alcohol is of little value on account of its direct dietetic value; but if it stimulates the flow of "appetite-juices" of the digestive apparatus, it indirectly becomes of important dietetic value by assisting the digestion and assimilation of food. Is a natural alcoholic beverage, such as pure wine, beer, or cider, taken in moderation with food, to be considered a poison to normal healthy people? If so, why do the vast majority of civilised people, who know perfectly well the evil effects of the abuse of alcohol, take it in moderate quantities? Why do they not prefer tea, coffee, and other stimulants? They appreciate and know full well the truth of what Shakespeare makes Cassius say—"Oh that man should put into his mouth a poison to steal away his brains!" Is it simply the force of a bad national habit and an evil example, as total abstainers who are satisfied with tea and coffee for stimulants would say? For they would cite the fact that experiments have been made by German professors on their students to show the evil effects even of small doses of alcohol in any form upon the mind; but the argument against any logical inferences being drawn from such experiments is that they are artificial and conducted under artificial conditions. It requires no series of experiments to show the effects of alcohol in large doses, for, as Maudsley¹ truly says, "A drunken man notably exhibits the abstract and brief chronicle of insanity, going through its successive phases in a short space of time. First, a brisk flow of ideas, inflamed emotions, excited talk and action, aggressive address, unusual self-confidence, a condition of stimulated energy with weakened self-control, so like the sort of mental excitement which goes before an outbreak of mania that the one is sometimes mistaken for the other; next, as in insanity, sensory and motor troubles, incoherent ideas and conversation, and increasing passion, which, according to the previous temperament, is expansive, quarrelsome, melancholic, or maudlin, and which may sometimes, as in

¹ "Pathology of Mind." Maudsley.

insanity owning no cause, go through these stages in succession in the same individual; lastly, a state of stupidity or stupor, which might be called, and is essentially, a temporary dementia."

Every physician knows the important influence of a happy and contented mind upon digestion, assimilation, and good bodily nutrition. If a moderate quantity of alcohol taken with food leads to good digestion waiting upon appetite—and by many thinking men this is the case—then it may serve to explain its widespread use. But at all times, and among all peoples, there has been a desire to be able to alter their mental reaction to their environment. What considerable part this has played in the human evolution of civilisation it is impossible to say. Archdall Reid¹ would say that the widespread resort of the individuals which make up a nation to alcohol or other stimulating drugs would eventuate racial immunity. Haycraft points to alcohol as a great agent in the prevention of the perpetuation of poor types, and there is much to be said in favour of this view if we regard all chronic inebriates as moral imbeciles, and therefore should be compulsorily segregable, although the law at present does not recognise them as such. Moreover, it will be shown beyond question that neuropathic and psychopathic degenerates, and criminals, lunatics, epileptics, and feeble-minded, under the influence of alcohol, in many cases even *in small and moderate quantities*, become actively anti-social, thus leading to their detainment in infirmaries, inebriate reformatories, prisons, and asylums. Still more obvious is it that all persons with a *locus minoris resistentiæ* of the nervous system, whether inherited or acquired, whether by injury or disease, are unable to withstand the effects of prolonged inebriety. They must either become anti-social or die from the effects of the drink. The survival of the fittest in the struggle for existence depends more and more upon mental capacity than physical strength. Natural selection thus always tends more and more to place the *locus minoris resistentiæ* of the individual in the nervous system, and

¹ Archdall Reid. "Alcoholism: A Study in Heredity."

in that part of the nervous system which has been latest evolved—the cerebral cortex, the seat of consciousness. If Nature made no failures, it would make no successes. Variations must occur; that inherent neuro-potential instability which may on the one hand in a well-balanced mind lead to constructive imagination and genius of the highest order—Nature's success—may on the other hand lead to epilepsy, insanity, degeneracy, and mental perversion—Nature's failures.

Between the two extremes is a wide and increasing class of eccentric and neuropathic individuals, often combinations of cleverness and crankiness, possessing imagination but lacking calm judgment, zealous, well meaning, and egotistical, but generally vain and unreasonable in their mental attitude towards those who disagree with them, noisily clamouring for rights when they should be attending to duties, bulking largely in the public Press: they fulfil a mission sometimes good, more often bad.

We may ask, Does alcohol act as a test of fitness and sift out the possessors of inherent unstable neuro-potential, eliminating those in whom will-power is deficient and therefore insufficient to control and restrain the readily excitable feelings and easily aroused passions of a neuropathic or degenerate stock?

Dr. Branthwaite, in the report previously referred to, cites some interesting facts respecting the birth rate and death rate of children born of married or widowed women inebriates. Referring to 352 women admitted to reformatories the chief points of interest seem to be:—

- (1) The large proportion of childless women amongst those married or widowed.
- (2) The large number of children born of those who are not returned as childless.
- (3) The high death rate of the children.

But then we find that out of the 318 persons committed under Section 1 of the Act, in 259 the committal was for unlawfully neglecting children in a manner likely to cause them unnecessary suffering.

Nearly 23 per cent. of the married or widowed women

were declared childless. Considering the class from which these women are drawn this would be surprising, were it not for the fact that the figures take no account of premature or still births. Excluding the forty-four childless women amongst the married and widowed, the remaining 149 have each given birth to an average of 7·4 children.

There is therefore a high birth rate and a high death rate; 92 women gave birth to 850 children, 45 per cent. dying in early youth or infancy.

The high birth rate and the high death rate are indicative of the effects of alcohol on conduct, the former may be explained by passion mastering prudence, and the latter by a lack of moral sense and degradation of maternal instinct as shown by the number of convictions for cruelty and neglect of children. I should believe this a more important cause of the high death rate than inborn bodily weakness. Dr. Carswell supported this opinion when discussing the subject of this paper at the Medico-Psychological Society, and he cited the success which had attended the removal of the children of drunken parents from their homes.

The large percentage of childless widows or married women probably is due to the more frequent incidence of venereal infection causing miscarriages and abortions, or sterility. A considerable proportion of the women dying in the asylums with a history of drunkenness show signs of syphilis or adhesive inflammation of the oviducts, which, in the great majority of cases, is of venereal origin.

White ("Alcoholic and Drug Intoxication," *Handbook of Medical Science*, vol. v., p. 81), has well said, "The causes of drinking are infinitely varied and intimately bound up in the heart of man, at once an expression of his strength and his weakness, his successes and his failures."

It is not my purpose to justify the use of alcohol on these grounds, but in my opinion its moderate use may act beneficially by tending to remove that prudence and selfishness which restrain the natural and spontaneous feelings of human sympathy and sociability which spring from the affective side of man's nature. We can thus understand how wine maketh glad the heart of man. But moderation

in one individual is excess in another, and it is easy to pass the line which carries from the region of safety into danger if alcohol is habitually taken as an article of food. Probably the teaching of Parkes is the correct attitude to take up on this question: "It produces effects which are often useful in disease, and sometimes desirable in health, but in health it is certainly not a necessity and many persons are much better without it. As now used by mankind *it is infinitely more powerful for evil than for good*; and though it can hardly be imagined that its dietetic use will cease in our time, yet a clearer view of its effects must surely lead to a lessening of the excessive use which now prevails."

In *La Revue* (February, 1903) the opinion of the leading French specialists is given upon the question, "L'alcool est il un veritable aliment?" The general consensus of opinion of the majority of these savants is that in a wine-growing country like France the *natural fermented juice* of the grape, taken in moderation, is not injurious, but even necessary for a people whose ancestors have dwelt in a wine-growing country from the earliest periods. But they are of opinion that the abuse of alcohol in the form of distilled liquors, essences, and fabricated wines, has had a most pernicious influence upon the people, causing alcoholism, with its mental and bodily defects, far more frequently than formerly.

THE INFLUENCE OF ALCOHOL UPON THE NERVOUS SYSTEM AS EXHIBITED IN THE POST-MORTEM ROOMS OF HOSPITALS AND ASYLUMS.

For a long time past I have been struck with the few cases of alcoholic liver that I have seen in the *post-mortem* room of the asylum as compared with my hospital experience in the wards and the *post-mortem* room. I can only remember seeing one case of hob-nailed liver with abundant ascites in my asylum experience, and this experience is very different to that which I have had in the hospital.

The case I refer to was that of Jane Cakebread, who was convicted nearly four hundred times before she was found incapable of taking care of herself and certified as

insane. She was a constant object-lesson to society of the inadequacy of control of the liquor traffic and of our law to deal with chronic inebriates, for she was not in the ordinary sense insane.

I came to the conclusion that, as a rule, only people with an inherently stable nervous system could drink long enough to acquire advanced alcoholic cirrhosis of the liver, and I therefore instituted a comparative inquiry of clinical and *post-mortem* results of patients dying in Charing Cross Hospital and Claybury Asylum. Dr. Candler, my assistant, has undertaken this, and I have told him not to be in any way biassed in his opinions by my theories, rather to err the other way. I will now give his results, but I may remark that I have been over his statistics and findings with him, and I can vouch for the fact that he has exercised the greatest care and diligence in making them as accurate as possible. The error of the personal equation comes in to a much less degree in collating the *post-mortem* results, for at the asylum the notes have been made by two or three skilled pathologists in a systematic manner; at the hospital, although the notes are not so systematically kept, so that in a few instances the weight of the liver is not mentioned, yet they are the records of skilled pathologists whose opinions are authoritative. Moreover, in a number of instances the opinion of hepatic cirrhosis was confirmed by microscopic examination. As far as possible the *post-mortem* findings have been correlated with the clinical records. Here naturally we found the hospital notes more precise as regards the quality, the quantity of liquor taken, and the length of period of alcoholic indulgence.

A COMPARATIVE INQUIRY INTO THE INCIDENCE OF CIRRHOSIS OF THE LIVER AT CHARING CROSS HOSPITAL AND CLAYBURY ASYLUM RESPECTIVELY DURING THE LAST SIX YEARS. BY J. P. CANDLER, M.A., M.B. (Cantab), D.P.H.

At the request of Dr. F. W. Mott, I have recently examined the clinical and *post-mortem* registers of Charing Cross Hospital and Claybury Asylum for the past six

years, with the view of ascertaining the number of cases of hepatic cirrhosis which have been recorded during this period.

I have also drawn up a table of comparison between the cases which have occurred at each institution, and have added some figures taken from a paper by Drs. Rolleston and Fenton of St. George's Hospital. This table is only intended for general comparison, the number of cases being far too few to serve as accurate statistical evidence.

Several features of considerable interest have been elicited as a result of the inquiry, which I will endeavour to record as concisely as possible.

At Charing Cross Hospital the autopsies upon 1099 adult cases were examined, comprising 735 males and 364 females; out of this number there were 85 cases of hepatic cirrhosis recorded (males 77, females 18).

At Claybury Asylum 1271 cases were examined (627 male, and 644 female); of this number only 23 cases of hepatic cirrhosis were found, 14 being male cases, and 9 female.

Drs. Rolleston and Fenton's paper¹ is devoted to the consideration of 114 cases of hepatic cirrhosis extracted from the *post-mortem* records of St. George's Hospital for the ten years prior to the publication of their paper in 1896.

The points to which I would draw attention in connection with the cases examined at Charing Cross Hospital are:—

(1) Hepatic cirrhosis appears to be commoner in males than in females (*cf.* St. George's Hospital figures).

(2) Death from cirrhosis of the liver in the case of females occurs at a slightly earlier age than in males (*cf.* St. George's Hospital figures).

(3) There is very little difference between the ages of those dying from cirrhosis of the liver, and those dying from other diseases, although suffering from cirrhosis.

¹ "On the Cirrhotic Liver," by H. D. Rolleston and W. J. Fenton, *Birmingham Medical Review*, 1896.

This is stated by Dr. Rolleston to be contrary to the experience of Dr. Hilton Fagge at Guy's Hospital, though it was found to be the case by Dr. Rolleston and receives confirmation from the records of Charing Cross Hospital.

(4) In the greater proportion of cases at Charing Cross Hospital the cirrhotic liver was found to be enlarged at death, and the average weight of all the livers showed an increase over the weight of the natural healthy organ. In only three cases was the size and weight of the liver so decreased as to resemble that of the small "hob-nail" variety.

(5) Reference to the table shows that enlargement of the liver was accompanied by an increase in the average weight of the spleen, and it will be seen that the figures quoted show a great similarity of the weights of the two organs recorded from each hospital. With respect to the weight of the spleen in cases of hepatic cirrhosis it is to be remembered that this organ, even in health, is liable to great variations, and Dr. Rolleston states that "the extreme enlargement seen in some cases of cirrhosis is probably . . . due to some concomitant toxæmic condition. It may be safely said that in cases fatal from cirrhosis, the weight of the spleen does not bear any constant relation to the weight of the liver."

(6) There appeared to be no relation between the size of the liver and the amount of ascitic fluid found in the abdomen, as much fluid being present in cases where the liver was enlarged as in those where it was found diminished in size and weight.

(7) The amount of ascitic fluid found at the autopsy was in many cases enormous, amounting in one or two instances to two or three gallons. In 17 out of the 82 cases there was a history of the performance of paracentesis abdominis prior to death, an operation which, in two or three instances, had to be repeated on five or six occasions. The necessity for this was evidenced more in the case of the males than the females.

(8) Of the 82 cases, peripheral neuritis of alcoholic origin was recorded in 4 (2 males and 2 females), and

was stated to have been the cause of death. These figures agree with those of Dr. Rolleston, who records three instances of peripheral neuritis in females in his series of 114 cases; in each instance this was stated to have been the cause of the fatal termination. He states that "In only three cases was death due to peripheral neuritis of alcoholic origin. Since the two diseases are so frequently due to the same underlying cause, *i.e.*, alcohol, it might, *à priori*, have been expected that they would frequently coincide. This, however, appears not to be so."

(9) It is worthy of remark that no less than 12 of the 82 cases (11 male, 1 female), met their death as the result of street accidents, while 10 were admitted to the emergency wards suffering from some intercurrent disease, and death took place a few hours or days after their admission. Cirrhosis of the liver was found at the autopsy in all of the 22 cases

(10) The incidence of tuberculosis in these cases of hepatic cirrhosis is very high, especially at St. George's Hospital, where the death rate from tuberculosis is far higher than that found at Charing Cross Hospital. Reference to the table will also show that out of the 19 cases at the latter institution in which the liver affection was associated with tuberculosis, only 13 showed signs of active disease.

(11) Congestive disturbances of the alimentary system, as evidenced by chronic gastritis, &c., were present in a large percentage of cases.

Investigation of the Cases of Hepatic Cirrhosis at Claybury Asylum.

Examination of the *post-mortem* registers at Claybury Asylum over the same period show a completely different condition, as regards the incidence of hepatic cirrhosis, to that found from the study of the registers of a general hospital. Briefly, the whole condition may be summarised by stating that whereas at a general hospital the tabulation of these cases was a comparatively simple matter, it was

a matter of great difficulty at Claybury to decide which cases could be accepted as showing definite cirrhotic changes, so ill-defined were they in most instances and so scarce in number. This will be at once evident when it is stated that of 1,271 cases examined only 23 could be accepted as showing definite cirrhotic affection. The points to which I would draw attention are:—

(1) The rarity with which a liver showing naked-eye appearances of cirrhosis is found at Claybury Asylum (23 out of 1,271 cases).

(2) The rarity with which definite and well-marked cirrhotic changes in the liver tissue are found at Claybury when compared with those found at a general hospital, the most marked alteration in shape and size having been associated with general arterio-sclerosis, and with general paralysis of the insane, where it is impossible to state definitely how much of the deformity has been produced by the effects of alcohol alone or is the result of the combined effects of alcohol, syphilis and arterial degeneration.

(3) The total absence at Claybury Asylum, during the last six years, of any case associated with ascites.

(4) During the same period there is only one instance in which cirrhosis of the liver has been assigned as the cause of death. In this instance the patient was 32 years of age, was a billiard marker, and had been admitted for homicidal and suicidal tendencies; he died after a residence of three months in the asylum.

(5) The relatively greater frequency with which acute and chronic gastritis and other inflammatory lesions of the stomach, are met with in cases of alcoholic affection of the liver among the insane. It is worthy of note that evidence of inflammatory changes of the mucous and submucous tissues of the stomach and small intestine are frequently met with at autopsy in all forms of insanity; this may be due, to some extent, to the ill-effects produced by the ingestion of foul saliva, a marked condition of oral sepsis being frequently found.

(6) The incidence of tuberculosis appears at first sight (*cf.* table) to be higher than either at Charing Cross or St.

	CHARING CROSS HOSPITAL			ST. GEORGE'S HOSPITAL			CLAYBURN ASYLUM		
	Males	Per cent.	Females	Males	Per cent.	Females	Males	Per cent.	Females
Total number of post-mortem examinations	735	..	364	*	..	*	627	..	644
" cases with hepatic cirrhosis	67	..	18	82	..	32	14	..	9
Number of cases with ascites ..	25	37.3	12	27	32.9	9	—†	..	—
" " without ascites ..	42	62.7	6	55	67.1	23	13	92.8	9
" " with a history of paracentesis abdominis	13	19.4	4	*	..	*	—	..	—
" " fatal from cirrhosis ..	24	35.8	13	29	35.3	18	1	7.2	—
" " diseases other than cirrhosis ..	43	64.2	5	53	64.7	14	13	92.8	9
Average age at death of cases fatal from cirrhosis ..	50.8 yrs.	..	47 yrs.	50.3 yrs.	..	46 yrs.	32 yrs.†	..	—
" " " diseases other than cirrhosis	46	..	48	48	..	45.6	51	..	46 yrs.
" " with ascites ..	49	..	47	*	..	*	—	..	—
" " without ascites ..	46	..	48	*	..	*	51 yrs.	..	46 yrs.
Number of cases associated with peripheral neuritis	2	2.9	2	—	11.1	3	—	..	2
" " fatal from renal disease ..	3	4.4	—	6	7.3	2	—	..	—
" " with gastric disturbances ..	28	41.8	12	*	..	*	13	92.8	7
" " arterio-sclerosis ..	1	1.5	—	*	..	*	5	35.7	1
" " a history of alcohol ..	25	37.3	8	64 (male and female combined)	..	..	3	21.4	5
" " associated with tuberculosis	19 out of 85 cases§	22.3	8	34 out of 114 cases	29.8	..	7 out of 23 cases§	..	30.4
" " fatal from tuberculosis ..	4	4.7	..	17	114	..	—	..	—
Average weight of the liver in all cases	67.5 ozs.	..	..	65.49 ozs.	..	..	54.3 ounces.	..	..
" " cases fatal from cirrhosis ..	67.4	..	..	63.17	..	..	—	..	—
" " diseases other than cirrhosis	67.4	..	..	67.19	..	..	54.3 ounces.	..	..
" " spleen in all cases ..	9.5	..	..	9.8	..	..	9.3 ounces.	..	..
" " cases fatal from cirrhosis ..	11.9	..	..	11	..	..	—	..	—
" " diseases other than cirrhosis	8.2	..	..	9	..	..	9.3 ounces.	..	..

* Denotes that the information is wanting. † One case. ‡ In one case there was a pint of fluid noted, but there was cardiac failure in this case. It will be observed that the age of the male insane patients is higher than that of the hospital cases, the reason being that a number of old men suffering with arterio-sclerosis under the influence of drunk are sent into the asylums. One striking fact was the much greater frequency of atheroma in asylum cases as compared with hospital cases. This may be explained by the fact that nearly half the total male cases in asylums are general paralytics. The relation of syphilis to general paralysis is probably associable with this result. § Of the seven female cases, only one showed active tuberculosis, the remaining six were cases of quiescent tubercle. Of the nineteen male cases, six were cases of quiescent tubercle.

George's Hospital, but in only one out of the seven cases was the disease in an active state ; moreover, the number of cases is much too small to allow of any definite statement on the subject.

(7) The greater frequency with which arterio-sclerotic changes are associated with cirrhosis of the liver in the case of the insane, especially among the males. In the six cases in which arterio-sclerotic changes were present, no patient was under the age of 60. In people who have passed the age of 60 vascular changes would be expected, yet it is a striking fact that among the insane generally, the evidence of arterial degeneration is seen at an earlier age and more strikingly manifest on the *post-mortem* table than among the sane.

The differences in the foregoing results are so striking that without claiming any precise scientific accuracy for these statistics it may be fairly deduced that my *à priori* premise is true. Alcohol in small or even moderate doses, and certainly alcoholic abuse even for comparatively short periods of time, as a general rule is sufficient to bring the epileptic, the imbecile, and the potential lunatic to the asylum long before he can drink enough to produce a cirrhotic liver.

I shall now compare the clinical differences of alcoholics in hospital and asylum practice. The people who are admitted into the medical wards of the hospital suffering with disease directly due to alcoholic abuse, are cases of delirium tremens, neuritis, with or without psychosis, dilated stomach and gastritis associated with hæmatemesis and enlarged liver, and cirrhosis of the liver with ascites, also heart failure, the patient being often in a dead or in a dying condition. Alcohol often is an important co-efficient in many other diseases for which patients are admitted, viz., arterio-sclerosis and degenerative processes accompanied or followed by chronic Bright's disease, cerebral hæmorrhage, and cerebral softening, bronchitis and emphysema with heart failure, fatty degeneration of the heart and vessels, coronary sclerosis with angina

pectoris, and aneurysm. Degenerative processes affecting the aorta and large arteries are most frequently the result of a combination of three factors, alcohol, syphilis, and occupation stress, but there may be also an inherent germinal deficiency.

Chronic alcoholism by devitalising the blood lowers the defences of the body against microbial invasion; consequently micro-organisms of pneumonia, tuberculosis and other specific germs of infective diseases, as well as the ordinary septic and pyogenic microbes, find a suitable soil. A slight general depressing influence, such as a chill or local injury, which would have no harmful effect upon a healthy individual even if micro-organisms were present—because the vital reaction of the living tissues would prevent a general infection—to a chronic alcoholic may be most dangerous and lead to fatal illness.

ABRIDGED STATISTICS OF NOTES OF 781 CASES ADMITTED
TO THE MEDICAL WARDS OF CHARING CROSS HOSPITAL
DURING ONE YEAR, 1905.

The notes of 781 cases have been examined; these include all classes of patients—*i.e.*, 375 males, 183 females, and 183 males and females under 20 years of age; deducting the latter, there remains 598 persons over 20 years of age. These have been divided into:—

(1) Alcohol as a direct cause.

(2) Alcohol as an indirect cause.

(3) Doubtful cases where in all probability alcohol has played a considerable part in the causation of the disease.

In the first class there were 48 cases—*i.e.*, 8·02 per cent.

„ second „ „ 48 „ „ 8·02 „

„ third „ „ 32 „ „ 5·03 „

Total 128 cases (111 males, 17 females) „ 21·3 „

Of these cases the heart and vessels were affected in 23 cases, the liver in 21, the lungs and pleuræ in 19, the kidneys in 12, the joints in 11, the stomach in 10, the nervous system, manifested by neuritis and generally mental trouble, was affected in 8, delirium tremens occurred in 5.

Occupation as a causal factor of intemperance was found to have a very considerable influence, for example:—

(1) Those who drink because their occupation makes them thirsty—as dustmen, stokers, labourers, Covent Garden porters, actors, stage carpenters, scene shifters, cooks, scullions, &c.

(2) Those who drink because it pays them in business—as publicans, those engaged in the wine trade, commercial travellers, &c.

(3) Those whose work brings them in contact with drink—as waiters, 'bus and tram conductors and drivers, draymen, cabmen, cellarmen, employees in distilleries and breweries, barmen, potmen, barmaids, prostitutes, &c.

ALCOHOL IN ASYLUM CASES, WITH AN APPENDIX OF CASES
ADMITTED TO HANWELL, BEXLEY, AND THE EPILEPTIC
COLONY, EWELL, IN THE YEAR 1905.

A large proportion of the recoverable cases admitted to the London County Asylums consist of pure drink cases, and of these 50 per cent. are discharged within three weeks to six months of admission. They often return again in a short time, and some cases, termed "recurrent mania" and "recurrent melancholia," are discharged and re-admitted many times, thus fictitiously raising the recovery rate. Many of these people would not come to the asylum were they not subject to the temptation of drink, for which they have an inborn or acquired intolerance. A certain proportion of the recoverable drink cases are delirium tremens, cases similar to those met with in hospital practice, but generally affecting persons of an inborn or acquired unstable nervous organisation; some of them, however, are pure drink cases sent to the asylum when nearly of sound mind, owing to the fact that the hallucinations and delusions have either entirely or nearly left them since the admission order was signed by the magistrate. The motor restlessness when they were admitted to the asylums may have proportionately subsided, and it would have been better for the individual and the ratepayer had such patients not been sent to the asylum. Such people may lose their employment if it is known that they have been in an

asylum ; it casts a stigma on their families ; lastly, it costs the ratepayers from one to several pounds for each case transferred from the infirmary to the asylum.

Leaving out these quickly recovering cases, there still remain a large number of cases of alcoholic insanity which may or may not have had previously symptoms of delirium tremens, but affecting persons of an inborn or acquired unstable mental organisation, epileptics, degenerates, imbeciles, potential lunatics, general paralytics, subjects of head injury, local brain disease, syphilis, and arterio-sclerosis ; in all such cases the symptoms caused by the poison are liable to be prolonged and even become permanently installed.

According to the predominant features of the mental derangement, cases are diagnosed "alcoholic mania," "alcoholic depressive mania," "alcoholic melancholia," "alcoholic dementia," "acute hallucinatory insanity," or as the Germans term it, "alcoholic hallucinosis," "alcoholic delusional or paranoidal insanity," "epileptic insanity," or "pseudo-paralytic insanity." If alcohol is the essential factor, however, in the production of the insanity there will be certain specific indications in all these varied forms of insanity pointing to the more or less specific action of the poison. Even in the absence of a history of alcoholic indulgence there are certain physical signs and mental symptoms which point to alcohol as the cause. The more certain these signs and symptoms, the more certain can we be that the cause is removable and the more hopeful the prognosis. These signs and symptoms are found most pronounced in the two conditions of mental and nervous disorder which occur in hospital practice, viz., delirium tremens and polyneuritic psychosis. The symptoms are in such cases the results of the more or less prolonged action of the poison upon a more or less stable nervous organisation—that is to say, drink is the essential cause. Although every form of mental derangement may be closely simulated by alcohol when an insane temperament is acted upon by a sufficient quantity of the poison, yet when alcohol has been an efficient cause in the production of the insanity there are certain indications in the character and constancy of the

illusions, hallucinations, and delusions, in the mental state, as regards orientation in time and space and loss of memory of recent events, in the existence of a purposeful motor restlessness impelled by the hallucinations and delusions, and in the existence of tremor. Moreover, alteration of the deep reflexes, tenderness on deep pressure of the muscles, anæsthesia, paræsthesia, and hyperæsthesia indicative of neuritic affection, are frequently present singly or combined.

The affection of the neural structures subserving kinæsthesia, both central and peripheral, has been pointed out by Bevan Lewis, and is evidenced, not only by the objective and subjective signs and symptoms of neuritis, difficulties of gait and station, in the performance of fine muscular movements, but probably also by the frequency of creeping, crawling, odious things being the subject of the hallucinations. It may be supposed, indeed, that the primary seat of the hallucinations of rats, mice, snakes, spiders, beetles, and bats, such frequent characteristic features of delirium tremens, may arise in the neurons subserving the kinæsthetic sense. Possibly awakened by peripheral paræsthesia, the kinæsthetic cortex revives, by association with the visual cortex, images of creeping, crawling animals, black, grey, and shadow-like, the images of which are projected outwards by the mind onto the wall or, in some instances, to the near point of distinct vision; hence the purposeful movements and psycho-motor restlessness occasioned by these terrifying visions which are so characteristic of acute alcoholic poisoning. The following case is instructive. A general paralytic was admitted with signs of *mania a potu* to one of the asylums; he saw black devils, which flitted round him and lighted on his nose, putting stinking things in his nostrils and mouth. When the effects of the alcohol had worn off he passed into a state of marked euphoria, and angels now came and moistened his lips with honey and put sweet perfumes into his nostrils.

Visual hallucinations, also of a terrifying character, are the spectres of dead persons associated with coffins, of burglars, of policemen and detectives, of men hidden in the

house, of people who follow, accusing the patient of crimes or indecency, and calling him opprobrious names. The visual hallucinations arise probably in the visual cortex and excite by association verbal auditory hallucinations. These terrifying hallucinations of vision and hearing may lead to the patient running into the street in a semi-nude state and being taken up by the police. The more systematised these hallucinations, and the more they tend to the development of fixed ideas of persecution while the mind clears up in other ways, the more certain can we be that the patient is of an insane temperament, and that the alcohol has been the exciting factor in converting a potential lunatic into a probable subject of chronic insanity.

The existence of hallucinations of smell and taste are rare ; generally speaking, they are strongly in favour of an insane temperament. The frequency with which delusions of poisoning occur is possibly, in some instances, due to an insane interpretation of the pains caused by dyspepsia, occasioned by acute and chronic gastritis. I am the more convinced that this hypothesis may be true in not a few instances by the frequency with which one finds *post-mortem* evidence of morbid conditions of the stomach in the insane. In some instances, no doubt, the compulsory swallowing of drugs to make them sleep, or to quiet them, has given rise to delusions of poisoning.

That insane interpretations of the pains associated with inflammation of the cutaneous nerves may cause dangerous delusions is shown by the following cases : Several women who had the physical and mental signs of polyneuritic psychosis had delusions that they were on fire, that they had been set on fire with torches, and one patient, who was not then paralysed in her limbs, tried to jump out of the window. The proof in this case that there was a neuritis was afforded by the fact that a bullous eruption occurred shortly after on the limbs and trunk, a condition which I have histologically shown to be due to a neuritis of the cutaneous nerves. Another woman tried to get bangles off her wrist that were not there ; she developed wrist-drop the next day. Neuritic pains may also be insanely interpreted as the work of electrical machines.

Perhaps some of the most characteristic delusions are those related to the sexual functions, jealousy and suspicion of fidelity of the husband by the wife, and the wife by the husband, which may end in murderous assaults. It must be, however, remembered that there is sometimes a basis of truth in these accusations. Not infrequently a woman takes to drink because of the cruelty or infidelity of the husband, and the converse is also true.

Women suffering with polyneuritic psychosis often have the delusion that a baby is in the bed. One woman saw two babies. The several hallucinations arouse appropriate auditory hallucinations; they hear the baby crying. This may in some instances be correlated with a recent miscarriage. In fatal cases of this affection, often known as Korsakoff's disease, I have observed the frequency of uterine and tubal disease, and this leads me to suppose that there may be a peripheral origin to this delusion. Again, women sometimes complain that they have been violated at night. The frequency with which married women have hallucinations and delusions about babies and, in their delirium, talk about babies, finds a parallel in the occupation delirium of men suffering with delirium tremens. The carman drives his horses, the publican serves and talks to his customers, and the actor performs his tragedy and shouts, "All the world's a stage," &c. But nearly all these hallucinations and delusions, especially auditory and visual, may occur in insanity in which there is no alcoholic factor. It is, therefore, difficult to decide simply by the hallucinations and delusions alone, whether alcohol is the cause. Should they persist *while the mind otherwise becomes clear*, it is probable that the case is one in which alcohol has only played a subordinate part and the outlook of chronic insanity is probable. This is all the more likely to be so if the hallucinations and delusions become systematised and there is a complete absence of any peripheral cause.

While the effects of alcohol are still operating there are certain signs of mental derangement which are very characteristic; the patient may be depressed or excited, according to his temperament. The majority of cases which come

to the asylums, who either do not recover speedily, or not at all, exhibit signs of mental depression, and the history of the case frequently shows that they drank because they were miserable, worried, and had lost their employment, or their money and business, or had family troubles. Not infrequently this has led to attempted suicide. These cases of mental depression may be associated with excitement and motor restlessness, and be termed "alcoholic mania," or the delusions of poisoning and melancholy may lead to their refusal of food, and they are termed "melancholia." The alcohol taken may be merely a co-efficient with other conditions, such as the critical periods of life, climacteric, combined with worry and trouble acting upon a potentially insane person. To ascertain whether alcohol is the essential cause of the insanity, it is desirable to look for those characteristic signs of alcohol poisoning found in delirium tremens and polyneuritic psychosis, and in proportion as these are present or absent we may gauge the probability of alcohol being an essential and efficient cause of the mental disorder. We distinguish between delirium tremens, so common in males as compared with females, and polyneuritic psychosis, in which the converse obtains, but it must be remembered that there is no hard and fast line between these two manifestations of nervous and mental disorder, the result usually of chronic alcoholism. I have seen cases of delirium tremens which, after the delirium had passed off, manifested well-marked symptoms of polyneuritic psychosis, and some cases of polyneuritic psychosis have symptoms like delirium tremens at the onset. This latter form of chronic alcohol poisoning may terminate in a permanent paralysis and contracture and marked alcoholic dementia, and the *post-mortem* findings in such cases reveal organic changes in the central and peripheral nervous system in measure proportional to the loss of function. Still, it is astonishing what improvement can occur in such cases if they are carefully nursed and properly treated to prevent permanent contracture and wasting.

Chronic alcoholism may be manifested in the patients' conversation in various ways. There is often a tendency to

wit and humour, the mental association is rather by rhyme and repetition of well-worn jokes, abusive epithets, and coarse, vulgar stories, than keen logical repartee. Again, boastful loquacity, untruthfulness, and the tendency to relate *pseudo-reminiscences*, is a common symptom of chronic alcoholism. Especially characteristic is the mental confusion associated with the narration of pseudo-reminiscences.

A boastful loquacity frequently leads them into trouble, and into being suspected lunatics with delusions of grandeur. Their conversation may show a great deal of mental confusion and a tendency to wander incoherently from one subject to another without logical sequence, displaying a marked forgetfulness of what they had uttered a few minutes before. If their attention can be obtained it cannot be maintained, and there is a tendency to repeat themselves. They will talk unreservedly and unceremoniously in a familiar manner with either inferiors or superiors. This tendency to confabulate is a striking feature of chronic alcoholism in its manifold aspects. Personal illusions and affixing wrong names to persons are very common. Patients suffering with mental derangement from chronic alcoholism frequently are unable to correctly name the place where they are, or give the correct date or even the time of the year. Often a patient will tell you that she came to the asylum yesterday when she has been there months. Women suffering with polyneuritic psychosis are particularly liable to this loss of orientation in time and place. They may even forget where they live, although they remember where they went to school.

Loss of knowledge, or perhaps, more correctly speaking, loss of recollection of events that happened since the patient had shown mental signs of the poisoning, is common in women with polyneuritic psychosis. One woman, a cook, with signs of syphilis, had been in Hanwell four months and told me that she came "last night." The curious part of her story is that she had been married twice; when her second husband visited her she believed him to be her first husband, who had been dead many years. Although this is strange it is not altogether unexpected, for it is the rule

that these patients, who are unable to revive in consciousness any recent events, yet are quite able to recollect all the events of their childhood and early life. A bookmaker who was suffering with chronic alcoholic dementia could not remember the name of the horse that won the last Derby, although he was told several times, yet he could repeat the winners for each year from West Australian up to a few years ago. Again, as showing the peculiar features of alcoholic poisoning, I may cite the following case: A woman at the climacteric period was admitted with alcoholic mania and suicidal tendencies. She was a good type physiognomically, although the flushed face with dilated venules on the nose indicated chronic alcoholism, to which she freely confessed. She said she wished to leave the asylum, there was nothing wrong with her, and the cause of her drinking was grief caused by the death of her husband, who fell in the dock and was drowned.

As many of these patients are not scholars I apply simple tests of memory, of attention, and of calculation involving simple judgment and reason. I applied the following tests to this woman, who was able to give a coherent history of her life and knew the date she was admitted to the asylum, how long she had been here, and where she came from. I said to her: "You want to leave the asylum?" "Yes," she replied. "Then you must remember the name of the superintendent; it is Dr. Jones." She struck up a rhyme, "Oh Mr. Jones, oh Mr. Jones, he broke his bones by falling over cherry stones. I then asked her to remember the name, which she said she would have no difficulty in doing.

I then applied the second test. "You are given half a crown, and you go to a shop to buy half a pound of tea at 1s. 6d. per pound and a pound of sugar at 2½d., how much change will you have?" She was quite unable to state the correct amount.

Again, they may be able to repeat the multiplication table correctly, but if you reverse the multiplication sum they will give wrong answers. Thus, they will give 7 by 5 correctly, but 5 by 7 they will make different. I now

returned to my previous question, "Who is the Superintendent?" She had quite forgotten. When I said, "Who broke his bones?" she replied, "Why, Mr. Jones," and finished the rhyme, but was unable to reason from it that that was the name of the doctor who would be able to discharge her. Another test which I have found useful for detecting slight mental impairment in cases that are recovering is that used by Marie in testing cases of aphasia.

Take three pieces of paper of unequal size. Tell them to carry out three separate and distinct operations for each piece. They will be able to carry out each order when given separately to them, but if before they commence any one, the orders for the three are given together, they will forget and carry out the orders imperfectly. Thus, tell the patient to fold up the large piece and put it in his pocket, the middle-sized piece to be folded and handed to you, and the small piece thrown on the floor. Whether it is the lack of power of attention or inability to recollect more than one order I know not, but the frequency with which failure occurs in alcoholic subjects shows mental impairment which is not discovered if any one order is given. With respect to this test I may remark that I recently had under my care in the hospital a case of polyneuritic psychosis complicated by syphilis, in which the patient on admission was apparently hopelessly demented, passing urine and fæces under him and showing marked mental confusion, tremors and paresis, yet withdrawal of the poison and energetic anti-syphilitic treatment for a fortnight led to a complete clearing up of the mental state, so that he performed this test correctly and also the calculation test. This made me think of the dictum of Dr. Savage, "With alcohol all things are possible." Another very severe case of paralytic polyneuritic psychosis is now under my care in the hospital and is making a most remarkable recovery.

BRIEF ACCOUNT OF THE STRUCTURAL CHANGES.

I have examined the brains of a considerable number of cases of polyneuritic psychosis, and I have been struck with

the fact that the brains are of good weight, of good convolutional pattern and do not show much evidence of thickening of the pia arachnoid membranes, increase of cerebro-spinal fluid or other obvious signs of cerebral wasting. The ventricles are not granular, except sometimes there may be a few granulations in the lateral sacs of the fourth ventricle. Microscopical examination shows some wasting of the tangential fibres and subpial glia cell proliferation and felting, but as a rule this is not marked. The fibre systems are otherwise well preserved. There is no marked glia cell proliferation in the cortex, and when sections are stained by Nissl method the cells of the columns of Meynert are not distorted or poorly stained, their apical processes are not cork-screwed, and there is no marked coarse change of the cortical neurons as in general paralysis. There is no lymphocyte and plasma cell infiltration of the membranes and perivascular sheaths. Are there any morbid microscopic changes pathognomonic of toxic polyneuritic psychosis? I maintain this clinical syndrome is not peculiar to alcohol; lead, arsenic and other toxic conditions produce similar symptoms and similar pathological changes, and it makes me suspect that they are not caused by the direct effect of the alcohol, but rather by auto-toxins the result of a deranged metabolism. I have examined microscopically the brains of a good number of alcohol cases and several lead cases, and in all of these cases where there was a pronounced neuritis there were characteristic changes affecting the large psycho-motor cells (*vide* fig. 2). The changes in these cells are similar to the changes in the anterior horn-cells of the spinal cord, and are very evident; the nucleus is large and clear, dislocated to the side, sometimes extruded altogether, and there is a marked cell chromatolysis. The Nissl granules may be almost entirely absent or only found at the periphery. Sometimes the cytoplasm is vacuolated or shows excess of pigment. I have found in a few cases, similar changes of the cells of the nucleus of the motor oculi. It may be asserted that these changes in the cerebral and spinal motor neurons indicate a toxic action upon the

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[illegible]

whole motor efferent path. Seeing that in extreme cases I have found diffuse degeneration in the crossed pyramidal tract, it may be concluded that these changes are not solely due to a *réaction à distance* due to destruction of the peripheral nerves. Still, if the neurons are to recover their specific energy we must afford them the necessary stimulus, and this can only be effected by preventing contracture and atrophy of the muscles by massage and passive movements. Examination of the sensory path in severe cases often shows profound changes in the posterior spinal ganglion cells and degeneration in the posterior roots and columns of the spinal cord. In one severe case there was a portion of the spinal ganglion destroyed and only a cavity left. It was the fifth lumbar ganglion, and there was glossy skin of the foot on that side and a trophic sore on the sole. Owing to fatty changes in the vessel walls hæmorrhagic extravasations may occur, resulting sometimes in pachymeningitis hæmorrhagica. The following is an illustrative case: An epileptic, who, ten years ago, had been admitted to Claybury Asylum, was discharged two years later. He came in for a small legacy, again took to drinking heavily and was taken to the infirmary in a semi-comatose, paralytic state. He was thought to be a general paralytic and was sent to the asylum, where he died the next day. An inquest was held, and it was a question whether he was in a fit state to be sent to the asylum. It was found *post mortem* that he had a large cirrhotic liver and gastric catarrh. He died, however, from cerebral compression, occasioned by a pachymeningitis hæmorrhagica interna. There was a *hæmatoma* of large size compressing the left hemisphere. It covered nearly the whole of the convexity and was nearly an inch thick in the middle. It consisted of a laminated vascular membranous bag containing fluid blood. The membrane forming the sac, examined microscopically, exhibited laminæ, delicate walled vessels, and crystals of hæmatoidin were beginning to form in it. The sac was filled with fluid blood which had recently escaped from the new delicate walled vessels of the membrane. I interpreted the *post-mortem* findings thus: The vessels of the membranes had become

diseased from chronic alcoholism, one of these had ruptured, probably during a fit, and set up a pachymeningitis hæmorrhagica. This condition had given rise to the symptoms which had led to his being taken to the infirmary, and the fact that he had been in an asylum before, combined with his paralytic and stuporose state, had led to his certification and transference to the asylum. On the way down a fresh hæmorrhage had gradually taken place from the newly organised vessels, causing coma and death. Cases are occasionally met with which show encephalitis hæmorrhagica *post mortem* (*vide* Case II., p. 478).

In two cases of delirium tremens I have found widespread Marchi degeneration as Bonhœffer did, but both of these cases were complicated by pneumonia, and I found evidence of fibrinous thrombosis of vessels and hæmorrhages about the basal ganglia which would have accounted for (in these cases at any rate) the widespread Marchi degeneration; I do not think this degeneration occurs in uncomplicated cases of delirium tremens. Occasionally alcoholic polyneuritic psychosis may complicate organic brain disease and lead to difficulties of diagnosis (*vide* Case I., p. 472).

Certain Types of Alcoholic Insanity.

It is a well-known fact that a person, in getting drunk, may either become excited, boastful and grandiose in his ideas and conversation, as the French term it "*vin gai*," or melancholic, maudlin and sentimental—" *vin triste*;" so the cases of alcoholic insanity fall into two groups. The majority of the cases are either mania (frequently with depression) or melancholia; but a few cases are exalted, boastful, loquacious, and have actual grandiose delusions so pronounced as to simulate general paralysis. In fact, these cases are often diagnosed as general paralysis, and no wonder, for in most cases of alcoholic poisoning, in the early stage, the pupils may be sluggish in their reaction to light, the facial expression altered, the tongue and lips tremulous, the speech often slurred and syllables may be left out, the handwriting tremulous; and not only may

the spelling be incorrect and the words cut up into separate syllables and letters and syllables left out, but marked mental confusion may show itself in the matter expressed. The knee-jerks are altered, sometimes exaggerated, sometimes diminished or lost. To these objective signs and symptoms must be added the symptoms of mental derangement. Loss of memory, loss of knowledge of time and place, hallucinations of sight and hearing, but most marked and perplexing in this class of case are delusions of wealth and grandeur, instead of delusions of persecution, and it is the existence of these grandiose delusions which so often leads to an erroneous diagnosis of general paralysis. The dementia is, however, not progressive; the pupils, although at first sluggish in reaction, are usually not unequal, and the patient does not babble unsolicited of his wealth and grandeur as a general paralytic does, but only on questioning does he exhibit such delusions. The symptoms most alarming in their similarity to general paralysis may entirely disappear and the patient be discharged recovered; not infrequently, however, the opportunity of examining cases of this affection arises from death by intercurrent complications—*e.g.*, pneumonia, dysentery or heart failure. The naked-eye and microscopic appearances are quite unlike those of general paralysis. Although the membranes may be opaque and thickened, there is but little wasting of the cortex; the floor of the fourth ventricle is not granular, or only slightly so in the lateral sacs. There is microscopically no disorganisation of Meynert's columns, and no evidence of lymphocytes or plasma-cells in the perivascular lymphatics of the cortex. The only definite microscopic change is some neuroglia-cell proliferation in the subpial and septal structures of the cortex, and replacement by it of the association fibres in the tangential and supra-radial layers. Generally there is evidence of chromolytic changes of the pyramidal cells and active proliferation of young glia cells.

Dipsomaniacs are occasionally brought to the hospital and asylum. These are persons who have periodic cravings for alcohol, who in the intervals lead a sober and respect-

able life. Suddenly, for no accountable reason save an unnatural and insane craving for drink, dipsomaniacs neglect their home and their business, take little food, do not attend to their personal care and comfort, and drinking continuously to satisfy their morbid craving, sink into the lowest depths of moral degradation, and for a time lead an unnatural and vagabond life. Some reason or other may bring such a patient to the hospital or infirmary, or they of their own free will return home, and in a short time recover and resume their normal life. A respectable photographer, with all the signs of delirium tremens, was admitted to the hospital under my care. He had a bottle of cyanide of potassium, with which he wanted to poison himself and wife. He had delusions that he was followed by a man named N——. A hypnotic gave him a long sleep, and when he awoke all his delusions had disappeared, and he told me that he was not habitually intemperate, but that during the last few years he had had periods of craving for drink which he could not overcome. In the intervals he hardly touched anything, and lived perfectly happily with his wife and family. Curiously enough, he had had a similar attack two years ago, and had been brought to Charing Cross Hospital, when he had the same delusion about being followed by a man named N——. He informed me that this man was dead, and that he had nursed him.

Epilepsy and Alcohol.—It is well known that epileptics are particularly intolerant of alcohol even in comparatively small quantities. The fits occur more frequently and are more severe, and it is certain that men who have even never had fits become epileptics in later life by the abuse of alcohol. I have observed both in hospital and asylum practice numbers of such cases; in some the epilepsy is the direct effect of the alcohol upon an inborn, potentially unstable, nervous system; in others it is the action of the poison upon a brain damaged by syphilis, arterio-sclerosis, or injury. One very interesting case of this was a soldier, who was entirely free from any hereditary taint, and who rapidly rose to be a non-commissioned officer; he acquired

in South Africa *multiple cysticercus cellulosæ*. He had several fits and was invalided home. About the worst thing possible was done for him : he was put in charge of a canteen, acquired habits of drinking, which eventuated in his developing alcoholic epileptic mania. He became a patient of Sir Victor Horsley, who discovered the cause of the multiple tumours he had. He is now in Hanwell Asylum, is quite rational and does not suffer with any fits while he is unable to obtain alcohol.

It is not, however, in respect to the motor fits that alcohol is so dangerous to epileptics and potential epileptics, but in respect to the development of an impulsive automatism, causing them to commit indecent acts, crimes of violence, murderous assaults, and attempts at suicide, of which they may have no recollection. Some of the cases, however, of homicide and of attempted suicide remember perfectly well, and the question of responsibility for their action arises (*vide* Report of Dr. Hubert Bond) in courts of law.

Many of these epileptics are quite sane when they have been in the asylum a short time, and have to be discharged ; frequently they are readmitted more than once owing to drink.

Other types showing intolerance to alcohol are imbeciles and degenerates. They are sometimes in prison, sometimes in the workhouses, sometimes in asylums, or inebriate reformatories. A good example among many I could cite is Case E. J., who was sent to hard labour for three months and six months ; subsequently he was sent to Hanwell, and he is there now, but he has been discharged and readmitted six times. In the statistics such cases bulk large in the recovery rate. It may well be asked, From what have such cases recovered ? Not infrequently the history shows that they belong to a family of criminals, lunatics, and feeble-minded. Also a considerable number of the prostitutes on the streets belong to the defective class, and it may well be asked, How many are brought there *by drink and failure to obtain employment* ?

CHRONIC ALCOHOLISM AND LEGISLATION.

All the evidence of the law courts, prisons, hospitals, and asylums point to the necessity of *educating the public conscience* to the terrible evils caused by alcoholic abuse, and nothing will attain the end so certainly as the movement instituted by Viscount Peel of enlisting the sympathy and support of that large section of the community who use, but do not abuse, alcoholic stimulants. The public conscience should be aroused to many of the existing evils of the liquor traffic and the necessity of temperance legislation to control the same. But that is hardly the purpose of this paper. We must confine ourselves to the discussion of the best means of dealing with the chronic alcoholic, who is not at present in the eyes of the law considered insane, but who, in my opinion, may be quite as anti-social and dangerous to the community as the certifiable lunatic.¹

Let us commence with the chronic inebriate who, if he does not manifest delusions, hallucinations, or suicidal tendency may nevertheless be dangerous to himself and others. The vicious indulgence of an unnatural craving for drink may cause the greatest poverty, misery, and despair of his wife, family, relatives, and friends; he is therefore anti-social, a moral imbecile with weakened and disordered will, and liable at any time to commit crime. It is desirable that such persons in all classes of society should be placed under control, whether they desire so or not. At present it can only be done by voluntary application.

Next, all drink cases admitted to the hospitals and infirmaries should be made to pay the expenses of their maintenance, by weekly deductions if they are not able to pay in one sum. There is no more reason why they should be let off paying some fine than the person who is charged with being drunk and disorderly at the police-court. If such people on discharge continue their drinking habits and

¹ I agree entirely with Sullivan (*loc. cit.*) in asserting that some affection of mind is the usual result of chronic alcoholism, but it is commonly moderate in degree, or if more intense is so transitory in duration, that it very frequently does not bring the drinker within the walls of the asylum. Such cases probably constitute the larger part of the mental affection due to alcohol.

do not pay the weekly sum to the relieving officer, other measures should be adopted. It might be asserted that the wife and family would suffer; but if a man is a chronic drunkard, too often the wife and family have to maintain themselves, and not infrequently the drunken husband takes the wife's earnings. Some more efficient means are required to protect the sober and industrious ratepayer from supporting the drunkard and his family. Committal to labour colonies would be preferable to sending such people to prison.

It would be desirable to extend the time of detaining drink cases before sending them to asylums. This could be done by receiving-houses associated with the asylums, or by making all the infirmaries of cities and large boroughs have proper acute insane wards, with properly qualified attendants.

In this way the pure drink cases could be separated more efficiently from the insane in which drink has been a co-efficient rather than the essential cause. I am informed that this is practised at the Bellevue Hospital, New York.

Lastly, it behoves society as far as possible to remove the temptation to alcoholic abuse. The secret tippling of women of all classes is a fruitful cause of nervous and mental disease, and it should be made a statutory offence for a grocer or dealer with an off-licence to supply any form of alcoholic beverage to a woman, while charging it up in his account under the head of groceries or other provisions.

We cannot hope that people engaged in the liquor traffic will remit the custom of allowing their employées a daily quantum of liquor; but steps could be taken to make it a statutory offence for a publican to supply with liquor anybody intoxicated while he was engaged in any occupation concerned with the public safety. So that publicans should not only *not be allowed* to supply drivers of motors when intoxicated, but all persons who are engaged in vehicular traffic. The publican who supplied the last glass to a drunken driver should be heavily fined.

The municipalisation of tramways will do much to prevent drunkenness by not allowing the tramcars to stop

opposite public-houses, as the buses universally do, and by not allowing their officials while on duty to go into public-houses. I am given to understand that conductors become intemperate by running into public-houses to obtain change or to dispose of excess of coppers. A bus conductor at Colney Hatch Asylum informed me that his drinking habits, which ended in his being sent to the asylum, were acquired by his going into the public-house at the end of each of his six out and six return journeys to obtain change. If this is a fact, it could easily be remedied. But the great remedy for intemperance is to provide something better than the public-house for the people's enjoyment and happiness.

HANWELL STATISTICS.

I have not only seen many of the cases at Claybury Asylum, but I wrote to the Superintendents of three other London County Asylums—Banstead, Colney Hatch, and Hanwell—to let me see cases which they considered were in the asylum on account of alcoholic intoxication. I was surprised how few really typical cases they could produce. No doubt their explanation was the correct one, that alcohol patients form a large proportion of the recoverable cases. At Hanwell, however, Dr. Ascherson, an extremely able clinician who has contributed a valuable article on alcoholic polyneuritic psychosis, examined with me a number of female cases which were termed alcoholic cases; we came to the conclusion that in a very large proportion of these patients alcohol was not the efficient cause of the insanity, but a co-efficient of less importance than the inborn temperament.

By the kind help of Dr. Sparkes and Dr. Daniel, who have charge of the male and female sides respectively at Hanwell Asylum, I have obtained the following statistics concerning admissions in 1905:—

Admissions: 230 males, 237 females; total 467.

Of the 230 males alcohol was the alleged cause in 44 cases = 19 per cent.; of the 237 females alcohol was the alleged cause in 32 cases = 13·6 per cent. Total 76, or 16 per cent.

Nine of the 44 male cases had suffered with previous attacks, or 20 per cent.; 9 of the 32 female cases had suffered with previous attacks, or 28 per cent. Total male and female cases with previous attacks, 24 per cent.

In 13 of the 44 male cases there was a family history of epilepsy or insanity=30 per cent. In 5 cases the family history was either not obtainable or not taken, so that probably it should amount to 35 per cent.

In 11 of the 32 female cases there was a family history of insanity=35 per cent.

In 17 males of the 44 there was a family history of drink; in 6 of these 17 it was combined with a family history of insanity.

In 7 females there was a family history of intemperance; in 2 of these it was combined with insanity.

In 17 of the total 24 cases with a family history of drink it was in the fathers; the mother was a drunkard only in a few instances, and then generally both father and mother were intemperate.

These statistics are small, but they tend to show that the sons follow the intemperate habits of their fathers rather than inherit a drink craving. I saw myself, personally, a large number of these cases, especially those which had not been discharged. I came to the conclusion that a much larger percentage of the males were pure drink cases than the females. Twenty-eight of the males might be put down as cases of alcoholic insanity—that is to say, alcohol was the efficient cause, or rather, that if alcohol was unobtainable these people would not have come into the asylum. In a large percentage of these, however, there was an hereditary taint, quite 35 per cent. Eleven of the 32 females were considered by Dr. Daniel to be pure drink cases. In 3 of the 11 there was an hereditary taint of insanity in the family; 8 of the male cases were described as delirium tremen cases; 19 of the 28 pure drink cases among the males were discharged within twelve months, thus:

MALES				FEMALES			
1 month or under	3			2 months or under	1		
2 months or under	5			3 " "	2		
3 " "	5			4 " "	4		
6 " "	2			5 " "	2		
4 remaining in asylum more than six months, but discharged within the year	4			6 " "	2		
Total	19			Total	11		

Six of the females are noted as having had polyneuritis, none of the males.

Various worries in business, domestic troubles, love affairs, head injury, brain disease, inherent instability, imbecility, criminal degeneracy, and intolerance of alcohol, as manifested by previous admissions to the asylum, are among the other causes which, together with a family history of insanity or intemperance, one or more of which conditions were associated with a history of intemperance in the patient, make it extremely difficult to decide how far the insanity was due to the effect of the alcohol and how far to other causes. Of one thing I am convinced—that in a large majority of these cases the alcohol is a co-efficient rather than direct cause, particularly in women. The purely alcoholic cases are especially those which have toxic affection of the peripheral as well as the central nervous system, and all cases of delirium tremens; which, as Bonhoeffer states, in the majority of cases occurs only in the subjects of chronic alcoholism.

ALCOHOLICS ADMITTED TO BEXLEY ASYLUM, 1905.

Classification of the Form of Mental Disorder on Admission of those Cases Admitted in 1905, whose Principal Cause was Alcoholic Excess.

Males 46				Females 38			
Mental disease				Males	Females	Total	
<i>Imbeciles who were admitted with—</i>							
Recurrent excitement	1	0					
Depression	0	4					
Delusions	0	1					
Stupor	1	1					
Epilepsy	1	0					
Acute alcoholic hallucinosis	1	3					
	4	9					
Epileptics	3	2	5				
Paranoia and delusional insanity (chronic)	4	1	5				
Primary dementia	14	6	20				
Polyneuritic psychosis	0	2	2				

Mental disease					Males	Females	Total
Alcoholic hallucinatory insanity admitted—							
Excited ..	..	..	..	..	1	..	5
Depressed ..	..	..	..	..	3	..	3
Deluded ..	..	..	..	..	4	..	4
Demented ..	..	..	..	..	4	..	0
					12	..	12
Manic-depressive insanity admitted—							
Maniacal (5 recurrent)	..	..	..	..	4	..	3
Melancholic ..	..	..	..	..	3	..	0
					7	..	3
Organic dementia ..	..	..	..	..	2	..	3
					2	..	3
Total ..					46	..	38
						..	84

Alcohol also played an important part in the etiology of a number of cases of general paralysis.

Bezley, 1906.

T. E. K. STANSFIELD.

In the above statistics, in which alcohol is considered to be the principal cause of insanity, it will be observed that out of 248 male admissions, alcoholic excess was the cause in 46 or 18·5 per cent., and out of 246 female admissions alcoholic excess was the principal cause in 38 or 15·4 per cent.; a total percentage on the whole of the admissions of 17 per cent. But when we look into these cases we find that thirteen were imbeciles, five were epileptics, and five were cases of chronic delusional insanity, and no less than twenty were primary dementia. It is fair to assume that a very considerable proportion of these cases were the subjects of an inborn tendency to insanity, imbecility or epilepsy. A history of alcoholic excess, but including those cases in which alcohol was not assigned as the principal cause, was obtained in no less than 30 per cent. of the total male admissions, and 18 per cent. of the total female admissions, which roughly corresponds to 25 per cent., or one-fourth of the total admissions in which alcohol has either been assigned as the principal cause, or an important co-efficient. Investigations of the careful summary supplied to me by Dr. Stansfield in which alcohol was considered to be the principal cause or associated factor, shows that there are but very few cases in which other causes are not associated, *e.g.*, congenital deficiency, syphilis, arterial sclerosis, general paresis, epilepsy, senility and the climacterium in women, not to speak of misery, worry and poverty. It is in my

opinion therefore extremely difficult, in the absence of a precise history of the duration and degree of the intemperance, to decide how far the morbid mental state is due mainly to alcohol or associated causes. It would appear from the clinical evidence and the progress of the case to recovery, that in many instances the alcohol was the most important cause; in others it was a co-efficient; and again in others it served as the spark to rouse into activity a latent insanity or epilepsy, and to increase the active neuronie destruction of general paresis. A striking fact about these useful records, and one which agrees with Dr. Branthwaite's experience, is the relatively few cases in which alcohol is not associated with some other factors.

THE RÔLE OF ALCOHOL IN THE ÆTIOLOGY OF EPILEPSY:

An analysis of the male cases admitted into the Ewell Epileptic Colony from its opening until December 31, 1905. By C. HUBERT BOND, D.Sc., M.D., Medical Superintendent.

The analysis has been restricted to males because the numbers of each sex at the Colony are purposely disproportionate, and the female admissions are as yet too few to admit of such treatment without serious fallacy.

Up to December 31, 1905, there had been admitted into the Colony 364 males. For the purposes of this analysis 185 have been excluded from consideration owing to their histories being defective, or, in a few instances, because they proved not to be epileptic. In the remaining 179 cases, I have myself obtained a personal and family history which is sufficiently complete and reliable to permit of their forming the basis of statistical inquiry.

In 70 cases out of 363, alcoholic excess was recorded as an ætiological factor in one or other of the following relationships:—

(a) *A family history of intemperance* in respect to the parents or grandparents of the patient, with an endeavour to elicit with certainty whether such intemperance in the parent existed prior to the birth of the patient.

(b) *A history of intemperance on the part of the patient,*

distinguishing (i.) the cases in which the alcohol appeared to induce the onset of the epilepsy from (ii) those in which the effects of alcoholic excess were manifested in cases already epileptic.

I have said above that in the 179 admissions selected for analysis, I satisfied myself that their histories were "sufficiently complete and reliable." But it is right to qualify that statement by remarking that it is, unfortunately, very exceptional to obtain a family history that can be regarded as at all exhaustive. Much freer access to the various relatives of the patient would be required than is at present at our disposal. My collection of cases, however, brings out forcibly what I have mentioned elsewhere, namely, that however prominent *alcohol* or other apparently principal factor is in the causation of epilepsy or insanity, its importance is dominated by the existence of an epileptic or insane *heredity*. The morbid hereditary influence of these two psychoses is frequently combined, and, in my opinion, an epileptic one has an import at least equal to, if not greater than, one of insanity. I therefore prefer to express their prevalence as a combined percentage. Expressed this way, it may be said that in about 39 per cent. of the admissions to the Colony one or more members of the family have been ascertained to be epileptic, insane, or both; but that, restricting this calculation to the cases in which the family history was fairly complete, this percentage becomes considerably raised. In the 70 cases in which there was a relationship to intemperance in alcohol, the percentage reached to no less than 54.

Cases with a family history of alcoholic intemperance, on the part of one or more of the two parents and four grandparents, numbered 35 (or 20 per cent.). But in only 13 was it certain that one of the parents had exceeded in alcohol prior to the birth of the patient. This, of course, in any such statistical inquiry, should be made clear for each case; unfortunately, as regards the grandparents, the necessary evidence is almost always wanting. In the cases where it is abundantly clear that the parental intemperance did not exist prior to the birth of the patient—and that

therefore the alcoholism could not, *per se*, be regarded as port of the ætiology of such cases—I do not consider that their influence is necessarily abolished; on the contrary, I regard them of much importance, and merely urge the necessity for their clear separation. Twenty of these 35 cases possessed also a family history of either epilepsy or insanity, or both, and in 13 instances alcoholic intemperance was ascertained on the part of the patient; in 9 of the 35 this personal intemperance and family history of epilepsy or insanity were mutually associated.

Cases with a history of alcoholic intemperance on the part of the patient numbered 48 (or 27 per cent.). Of these, in 18 instances the nature of the intoxicant was not distinguished; it was beer alone in 20, spirits alone in 1, and both beer and spirits in 9. Concerning the amount taken, I can give no reliable figures; but my cases have impressed upon me that, whether the epilepsy has been induced by alcohol (usually acting on a constitutionally unstable nervous system), or whether the alcohol has been indulged in by a person already epileptic, alcohol in quite small quantities can precipitate either a recrudescence of epileptic fits which have been in abeyance for many years, or homicidal and suicidal manifestations, often of a very frenzied character. My 48 cases afford no less than 22 examples with a previous history of these impulses.

Of these 48 cases in which there was a positive history of alcoholic excess on the part of the patient, there were 27 in which, in so far that the history pointed to their having been hitherto free from fits or symptoms of insanity, the epilepsy appeared to have been induced by the alcohol. But in 50 per cent. (13) it was ascertained that one or more of their relatives (exclusive of cousins and nephews) had been epileptic or insane. In the remaining 14 cases, apparently free from such family taint, the family history in respect of the grandparents was incomplete in 6 instances, thus: no facts were available as to 2 grandparents in two cases, as to 3 in another case, and as to all 4 in three cases. Furthermore, in appraising the blame that, on the evidence at hand, legitimately attaches to alcoholism (on the part of the patient) for the development of epilepsy in these 14

cases free from an epileptic or insane heredity, account must be taken of the following facts: in two cases the mothers, short of being insane, were of a neurotic and very nervous disposition, and one of these mothers had for years given way to over-indulgence in alcohol; in the case of the patient who was the son of the latter, the first fit followed immediately upon a severe fright; in four other cases one or other of the parents had been addicted to alcoholism; in four instances (one of which was the son of one of these alcoholic parents) there was a history of severe head injury shortly before the onset of the first fit; and in two instances (one of which was the son of another of these alcoholic parents) the patient had contracted syphilis.

These possibly contributory factors are enumerated by no means with a view to underrate the evil effects of intemperance in alcohol, but, on the contrary, with the object of emphasising the view I believe to be the correct one, firstly, that the most serious of its deleterious effects is its power to vitiate the stock; thus, given that a person is fortunate in possessing an absolutely sound and stable nervous system, in such an one the facts I think go to show that alcoholic intemperance acting by itself would rarely, if ever, produce epilepsy, but that he would transmit to his offspring a liability for epilepsy either to manifest itself in their developmental period or to be precipitated later on in life by alcoholic indulgence in turn on their part. And secondly, that while opposed to "intemperance" is "temperance," for the person already epileptic there can be no such thing as temperance in alcohol. He should throughout his life regard it as a poison having the power, even in small quantities, either to increase the severity of his malady, or to light it up afresh if it have, fortunately for him, abated, or, saddest of all, to be the means of his committing impulsive crimes, often of the most appalling nature.

I am unable to report in full the large number of cases, at least 100, upon which the clinical and pathological conclusions given in this article are based; but I have selected the two following:

PSEUDO-PARALYTIC DEMENTIA IN A CASE OF
CHRONIC ALCOHOLISM AND SPINAL DIS-
SEMINATED SCLEROSIS.

CASE I.—*Female, aged 38, married, confirmed drunkard since marriage fourteen years ago. Admitted to St. Thomas's Hospital for alcoholic paraplegia complicated with other nervous disease of obscure nature. A year later, after heavy drinking, admitted to Claybury Asylum with symptoms suggestive of general paralysis, death a month later. Naked eye and microscopic characters, lesions corresponding to Korsakow's psychosis. Insular gliosis of the posterior column of the spinal cord, extending through the cord as a solid rod, 2-3 mm. in diameter, from the second cervical to the ninth dorsal, and fading off above and below these points. There is a less defined sclerosis of the antero-lateral columns.*

C. B., aged 38. Admitted to Claybury Asylum, September 9, 1900. Died, October 10, 1900.

Medical certificate.—She is in a state of acute maniacal excitement, singing and shouting incoherent nonsense. She informs me that she is going to entertain enormous numbers of friends very lavishly. It is impossible to get her to converse rationally on any topic. She is noisy and restless, requiring isolation from other patients. History obtained from the husband a day after the death of the patient: There is no history of insanity in the family; the father was a chronic drunkard but became a total abstainer; the patient had one sister who does not drink and a brother who does. Patient was married to informant at the age of 24; she has drunk, mostly gin and whisky, ever since. Before she came to the asylum she had been drinking heavily. She had three miscarriages, then a child born dead, next two children who lived a few hours and a few days respectively, and then a child who survived and is now five years old. The husband denies venereal infection.

NOTES KINDLY SUPPLIED BY DR. SHARKEY, ST. THOMAS'S HOSPITAL.

C. B., aged 38. October 30 to November 22, 1899.

History.—A brother, aged 36, has been in Wandsworth Infirmary for four years with "paralysis," which came on gradually, beginning in legs and spreading upwards. It commenced after he had reached the age of 21. Patient had had five miscarriages and four children born alive, one of whom is now living. She was admitted to Adelaide Ward six weeks ago, and remained a fortnight. About four months ago began to feel weakness in her legs with pricking pains; also involuntary "jumpings" of her

feet and toes. She had also pain in her eyes and some dimness of sight, a dull headache and some loss of memory.

Examination. Motor.—The gait is spastic in character, the legs being held rigidly and the toes dragging at each step, the foot being slightly inverted. The heels are brought down forcibly; has considerable difficulty in maintaining her equilibrium when told to turn round; Romberg's sign is present. The muscular power is very fair in both arms and legs. There is marked "intention tremor" in the legs when the patient raises them from the bed, and the same is present, but in a much less degree, in the arms. Coördination in the arms is scarcely at all affected, such movements as touching the nose with the fore-finger being well performed. The grasp on both sides is good, and the small muscles of the hand are normal. There is no weakness of the facial muscles. The movements of the eyes are well performed with the exception of internal rotation of the right eye, which appears to be slightly limited. There is no nystagmus. The tongue is protruded straight. There is no apparent muscular wasting.

Sensory.—Cutaneous sensation seems to be unaffected, although patient states that there is slight numbness from the knees downwards on both sides. No hyperæsthesia. The sensation to heat in the feet is blunted, and cold is not appreciated as such.

Reflexes.—Knee jerks brisk. Plantar reflexes difficult to obtain, especially on the right side. The contraction of the tensor fasciæ femoris was also more readily obtained on the left side. Ankle and patellar clonus not obtained, nor abdominal and epigastric reflexes. Pupils react to accommodation and light. Some incontinence of urine; sphincter ani not affected.

Special senses.—Taste as tested by quinine, sugar and salt appears normal. Hearing fairly good.

Other organs no sign of disease; the second cardiac sound at the right base is slightly accentuated.

October 31.—Put on pot. iod., grs. 10 t. d. s.

November 5.—Pains in legs are better; some dull pain in head, suffers from sleeplessness. Urine normal. There is still slight incontinence; a catheter passed this morning, but there was no residual urine.

November 4.—Ophthalmic examination by Mr. Lawford (pupils atropinised). Right surface of disc fluffy and indistinct; slight general pallor of disc; vessels about normal size. Left disc decidedly pale, especially in temporal half; surface is less blurred than that of right. Vessels not appreciably altered in size.

November 6.—For two days has noticed pricking and burning sensations in hands, especially after touching or grasping anything.

November 9.—The fields of vision were taken yesterday; they were both reduced.

November 10.—Feels stronger, was up yesterday and walked the length of the ward.

November 13.—Much better and stronger in every way; the "jumping" of the legs has also decreased, headache much better.

November 21.—Sight of left eye still imperfect.

November 22.—Discharged.

CONDITION ON ADMISSION TO CLAYBURY ASYLUM—CASE BOOK NOTES.

Tongue coated; teeth fair; bowels costive; heart, pulse and lungs, normal; pupils, left greater than right, both react sluggishly to light and accommodation; her gait is somewhat shaky, she pretends (*sic*) that she cannot stand, but she can really walk fairly well; knee jerks, left absent, right normal.

Mental condition.—She is the subject of alcoholic mania, with symptoms pointing to general paralysis. She has exalted delusions that she is Lady B., and that she possesses mines in Klondyke, that she is able to walk twenty miles before breakfast, that her jewels are of great value. She converses in an incoherent manner, is dirty and noisy, is in impaired health but fairly well nourished. Her gait is feeble and her calves tender on pressure.

The disease ran a rapid course and she died one month after admission.

The salient points of the *post-mortem* examination were as follows: The muscles were flabby and pale in colour generally. The brain showed thickening of the pia-arachnoid membrane over the parietal and central convolutions. Each hemisphere weighed 485 grammes and the membranes stripped without decortication. There is some atrophy of the central and frontal convolutions on both sides. The grey matter of the cortex is only slightly diminished—2.2½ mm. in depth. The striæ are indistinctly seen. The lateral ventricles are neither dilated nor granular. The pituitary body is a little larger than normal. The cerebellum, pons and medulla weigh 155 grammes, the ependyma of the fourth ventricle is a little granular in the lateral sacs.

Heart.—Substance soft and greasy, fatty degeneration. Valves healthy.

Lungs.—A little emphysema.

Liver.—1,055 grammes, very congested, fibroid and fatty.

Kidneys.—Pale, congested.

Intestines.—Granular colitis affecting the large bowel; no ulceration, but microscopical examination showed œdema and acute round-celled infiltration of the mucous and sub-mucous coats.

Cause of death.—Dysentery; granular variety.

MICROSCOPIC EXAMINATION OF THE ORGANS AND TISSUES.

(1) *Tissues stained by Marchi Method.*

Heart.—Shows extensive and marked fatty degeneration of the muscular fibres, especially are the muscoli papillares and the sub-endocardial fibres affected.

Kidneys.—Show fatty degeneration of the epithelium of the convoluted tubules.

Central nervous system. Spinal cord.—There is a scattered recent degeneration throughout the antero-lateral and posterior columns, but the degeneration is especially marked in the crossed pyramidal tracts of both sides. The cervical, dorsal, and lumbosacral regions were examined. There is no evidence of recent degeneration in the anterior and posterior roots.

Brain. Medulla oblongata.—Shows a scattered degeneration in the pyramids and the restiform bodies.

Cortex.—Frontal region: Broca's convolution and ascending frontal and parietal convolutions all show numerous scattered recently degenerated fibres. A striking characteristic is the appearance of blackening in all the cells of the cortex, especially the large Betz cells and the cells of the pyramidal layer. This is due to the action of the reagent upon a yellow fatty substance, which is considered to be pigment when stained by other methods. Hæmorrhages into the sheaths of the vessels, and occasionally into the brain substance, were found in some of these sections. Many of the vessels were apparent under a low power owing to the black appearance of the cells in their walls and in the lymphatic sheath. Some of these cells are endothelial cells undergoing fatty degeneration, others are leucocytes taking up the fatty particles of the degenerated nerve tissue.

(2) *Sections of the Brain and Spinal Cord stained by Marchi-Pal Method.*

Brain.—The frontal, ascending frontal, ascending parietal, and Broca's convolutions all exhibit a marked atrophy of the tangential fibres, and to a less degree, but very considerable, of the supra-radial. In some sections of the ascending parietal the tangential fibres were entirely absent. This was not due to a failure in the stain.

Spinal cord.—To the naked eye, the sections at all levels show a gliosis in the posterior columns, but from the second cervical to the ninth dorsal segment, a solid rod of unstained glia tissue with conical ends can be seen in transection; in the greater part of its extent it measures from 2 to 3 mm. in diameter, but it gradually tapers off above and below to 1 mm. Above, at the apex of the

calamus scriptorius, this sclerosis shows itself by an increase of glia tissue along the median fissure around the central canal. At the lower end of the cord there is a prolongation of the gliosis around the posterior median fissure occupying the median oval area of Flechsig in the lumbo-sacral region, and even extending down into the conus medullaris. In the mid-dorsal region the gliosis has invaded the base of the anterior at its junction with the posterior horn considerably more on the left side than on the right. The fibres entering Clarke's column are markedly affected, and there is a complete absence of the brush work of myelinated fibres around the cells of the column. This no doubt accounts for the Romberg's symptom noticed when she was a patient at St. Thomas's Hospital.

(3) *Spinal Cord Stained by the Iron Alum and Eosin Method for Glia Tissue.*

This area of gliosis shows transections of axis cylinders, many of which, however, are attenuated and atrophied; transections of fine glia fibrils, also numbers of nuclei and small vessels with much thickened walls are seen. The sclerosis is not vascular, and there are no signs of hæmorrhage or cavitation. The lesion corresponds to insular spinal sclerosis. There is in the antero-lateral columns, as the photomicrograph shows, a well-marked, diffuse, patchy sclerosis, most marked in the cervical and dorsal regions; it does not correspond to any definite system or tract of fibres, although it involves the crossed pyramidal tracts. The gliosis seems to spread out from the central grey matter, sparing the peripheral fibres of the cord. In no other part of the nervous system could an insular sclerosis be discovered by naked-eye examination. The cord throughout is much smaller than natural, not being larger than that of a child. This may be due to the sclerosis, but the grey matter itself is deficient, and the appearances suggest a congenital deficiency of certain groups of neurons with a proliferation of the embryonal neuroglia tissue. The sclerosed tissues stained by Weigert-Pal or Marchi-Pal methods show, as the photomicrograph illustrates, a white patch in the posterior column; at the circumference this patch gradually merges into healthy tissue, and more fibres with myelin covering can be seen; in the centre there are no fibres left with a myelin covering, consequently, the substance is quite unstained by these methods. Stained by Van Gieson, polychrome, Nissl or Mallory methods, the island of sclerosis is seen to consist of transections of axis cylinders without any myelin sheath; there is a narrow clear ring, however, round the fibre, owing to a shrinkage of the neuroglia substance, which appears as a fine dotted reticulum; in the minute round and oval spaces are the attenuated axons; the degree of attenuation varies. Vessels are

seen mostly cut in transection with thickened walls, but there is little or no evidence of inflammatory reaction. It seems likely that the brother who, in the hospital notes, is said to be in Wandsworth Infirmary, is suffering from a somewhat similar congenital defect of the spinal cord, causing paralysis of the lower extremities.

(4) *Examination of the Cerebral Cortex, the Grey Matter around the Aqueduct of Sylvius, Medulla, and Spinal Cord by Nissl, Polychrome and Eosin Method.*

The vessels were congested and hæmorrhages from rupture of small vessels and capillaries were found. There was endothelial cell proliferation of the capillaries, but no lymphocytes or plasma cells were found in the sheaths of the vessels as in general paralysis.

The large motor cells in all the regions enumerated above were more or less severely affected.



Photomicro Mid-dorsal region. Magnification 5.

The changes were those met with in undoubted pure cases of alcoholic polyneuritic psychosis. The condition of the cells was as follows:—The nucleus large, clear, and usually eccentric. The cytoplasm showed frequently a diffuse staining with crumbling edges, absence of Nissl granules and processes broken off up to complete disintegration; or in cells less severely affected there was a central perinuclear chromatolysis with Nissl granules only imperfectly seen at the periphery of the cell, and, in the dendrons, at their bases. Many of the cells show a great excess of yellow pigment for the tissues of a person of this age. *The groups of large and small cells of the oculo-motor nucleus exhibit these changes remarkably well, and this would account for the sluggish reaction of the pupils.*

The pyramidal cells of the cortex and the Betz cells show these changes in a more or less marked manner, but, unlike general paralysis, there is not a distortion of the columns of Meynert.

There is some excess of glia nuclei, and clusters may sometimes

be seen adhering to the degenerated cells. In the superficial layers of the cortex there is an excess of the large branching mesoglia cells forming a feltwork.

CASE II.—*Female, aged 36, single, polyneuritic psychosis in a chronic gin drinker; no noteworthy change in the liver to the naked eye, but considerable microscopic change. Death from heart failure. Degeneration of vagus nerves.*

J. B., single, age 36, machinist. Admitted Charing Cross Hospital, August 30, 1899, died September 4, 1899.

Past history.—Has been a gin tippler for years. One month ago she fell and bruised her back. She continued to get about until one week ago; her legs became weak, speech altered and she became drowsy.

Condition on admission.—She is very drowsy; answers in a very rambling manner at times. Speech slow and thick, reminding one of a drunken person. She is capable of answering yes or no, but in a long sentence generally rambles off. Her memory is very defective. She can remember long-standing events, but has no recollection of recent facts even a few minutes after having been told them. Tongue red, not tremulous. Breath very offensive.

Face.—On showing teeth, naso-labial fold is less marked on the left side, indicating facial paresis.

Eyes.—Pupils equal; they react to light sluggishly.

Legs.—There are minute hæmorrhages over the dorsum of both feet. Muscles of legs flabby. No wasting visible. Knee-jerks lost. Plantar reflexes lost. Complains of numbness of the calves. Great tenderness of muscles of calf and thigh on firm pressure.

Arms.—No wasting or paralysis. Great tenderness of muscles on pressure.

Chest.—Heart and lungs normal.

Abdomen.—Minute hæmorrhages upon skin of abdomen. No liver edge can be felt. No increase of dulness. No enlargement of spleen.

Electrical.—Legs. Faradism: Excitability to Faradism in both legs greatly diminished—more so in left than in right. Thigh muscles worse than those of legs. Contractions somewhat sluggish. Galvanism: In both legs—Anterior tibial group A.C.C. > K.C.C. In other muscles K.C.C. < A.C.C. In muscles of left thigh and vastus internus of right no contraction can be obtained. Arms and face normal.

September 1, 1899, Notes (by Dr. Mott):—

Body well nourished. *Pupils* equal, react to light and accommodation. No loss of control over sphincters.

Legs and arms.—Use of both lost. No wasting. Superficial and deep reflexes absent in legs. Foot drop and marked muscular

hyperæsthesia. Muscles respond to strong faradic current, some groups of muscles, especially left anterior tibial, A.C.C. < K.C.C. She has double vision, left internal strabismus, and slight facial paresis on left side.

Mental condition.—She is drowsy and somnolent; replies to questions, but in a drowsy almost inaudible manner. It is difficult to understand what she says partly on this account, partly owing to slurring and elision of letters and syllables. Her knowledge of time and place is most defective. She does not know that she is in Charing Cross Hospital, but thinks that she is at York Road Lying-in-Hospital. She does not know the day of the week or the month of the year. When told that it was September 2 she could not remember the date for a minute, even although it was repeated several times. She is able to tell of her birthplace and where she went to school, but her memory for recent events is almost entirely gone.

Cardiac.—The pulse is frequent, feeble, quick and irregular in force and rhythm. The heart impulse can be felt in the fifth space nipple line, area of impulse size of half crown, no thrill to be felt, no murmur to be heard, but the sounds are soft and indistinct.

September 4, 1899.—Patient became quite unconscious last night. Takes food very badly. Is still conscious of pain, as on pressing legs or arms screws up her face. Naso-labial fold more marked on right side.

Ten a.m.—Breathing full and deep this morning (? paralysis of diaphragm). Respirations 34. Slight cyanosis. Pulse 130, irregular, weak. Incontinence of urine and fæces. Temperature last night 101°. This morning 100°. Breathing became worse, cyanosis deepened and she died suddenly at mid-day.

Post mortem twenty hours after death. Body well nourished, no bruises, no *post-mortem* stainings.

Chest.—Well formed.

Lungs normal. Slight hypostatic congestion of the bases.

Heart, 8 ozs. No valvular lesion. Almost empty, with musculature very flabby. Slight atheroma of aorta, and thickening of aortic valves, but no incompetence. Coronary arteries patent. Heart substance mottled, pale, very soft and friable, obviously fatty.

Liver, kidneys and spleen showed no noteworthy naked-eye change.

Brain.—Dura mater not adherent. Longitudinal sinus, no clot. Pia arachnoid opalescent, separated from convolutions (over frontal and central convolutions especially) by fluid. Strips without erosions. Convolutions generally somewhat wasted apparently, as judged by depth and distension of membrane by fluid.

Ventricles slightly distended with fluid. No granulations. Scattered over various portions of the cortex were small areas of pia arachnoid congestion and hæmorrhage. Cortex when sliced into, exhibited little black points, due either to hæmorrhages or distended vessels.

There was nothing else noteworthy in the central or peripheral nervous systems visible to the naked eye. The skeletal muscles generally appeared paler than normal.

The mucous membrane of the stomach was covered with greyish tenacious mucus. The viscus itself was dilated; there was no acute congestion of the mucous membrane.

The large intestine showed in the mucous membrane little swollen, solitary lymphoid follicles, the size of a large pin's head. There was no congestion or ulceration.

On cutting up the brain, after hardening in formaline solution, various small areas, the size of a shilling to a florin, were found in the cortex, exhibiting the appearances met with in recent red softening due to venous thrombosis: viz., a thin layer of blood beneath the pia arachnoid and the cortex, with the white matter immediately subjacent, permeated throughout with little dark blue or black points. Areas of this nature were found on the upper border of the mesial surface of the right hemisphere, about the centre, in both central regions of the external surface and over the left parieto-occipital fissure.

Examination of Organs and Tissues (Marchi Method).

Heart.—Very marked subendocardial fatty degeneration of fibres; the whole of the remaining muscle substance shows a degenerative change, the fibres being broken up into short lengths, and the nuclei stained brownish-black, indicating advanced brown pigmentation or fatty degeneration of the nuclei.

Kidneys.—The convoluted tubules are all stained by the osmic acid, the epithelium being filled with fine black granules; scattered about, however, are portions of tubules in which the epithelium is obviously undergoing fatty degeneration, for the epithelium is intensely black with varying sized globules of stained fat.

Liver.—The organ is intensely congested and there are many hæmorrhages. The liver cells are atrophied and infiltrated with fat. There is a considerable amount of fibrotic and nuclear proliferation of the portal and interlobular connective tissue.

Spinal cord.—There is recent slight scattered Marchi degeneration in the posterior columns of an intensity sufficient to be recognised with a hand lens. There are a few degenerated fibres in the pyramidal system, direct and crossed, but none elsewhere.

Cortex.—There are a very few recent degenerated fibres in the white matter of the ascending frontal and parietal convolutions.

Skeletal muscles.—There is a marked fatty degeneration of the *tibialis anticus* and other muscles of the leg.

Nerves.—The phrenic nerves do not show a Wallerian-degeneration, but the myelin stains more than a normal nerve would do. There are many black granules scattered about due to leucocytes containing oleic fat. In transection no degenerated fibres are seen.

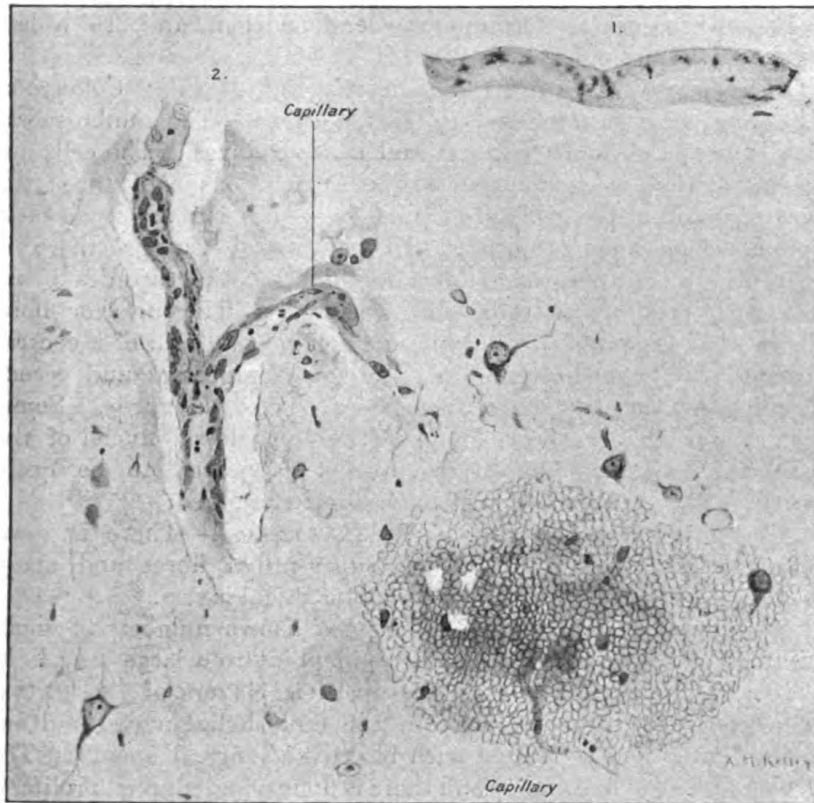


FIG. 1.—Shows the naked-eye appearance of the hæmorrhages in a section of the cortex.

FIG. 2.—Shows a small vessel which has ruptured, giving rise to a hæmorrhage. The vessel shows nuclear proliferation. Magnification 250×1 .

Longitudinal, transverse, and teased sections of the vagus show a similar appearance of many of the fibres, but here the degenerative process is more advanced, for, in numbers of the fibres, the myelin has broken up into black stained globules, which occupy a segment of the nerve, and then sometimes the same nerve can be traced above and below without this change, so that it is not an

ordinary Wallerian degeneration we are dealing with. This explains why a transection shows such a few black granules that it might pass for normal, the black granules seen being accounted for by accidental circumstances. The destruction of one segment of a nerve would lead, however, to as much functional disturbance as regards conductile properties from the controlling centres, as if the whole nerve were destroyed. Not so, however, as regards capacity for regeneration. Sections of the anterior and posterior tibial, ulnar, and peripheral nerves show a marked proliferation of the connective tissue forming the endoneurion, and, to a less degree, of the perineurion.

The Spinal Ganglion, Spinal Cord, and Medulla Oblongata, stained by Nissl method and its modifications.—The lumbo-sacral spinal ganglia all show chronic and acute changes. The cells are pigmented, there is a deficiency of chromophilous substance; the edges of many of the cells are crumbling; in some the nucleus is swollen, clear and eccentric. In the sacral ganglia there is apparently a disappearance of ganglion cells, the capsules being filled with proliferated cells and leucocytes. The anterior horn cells in this region show chronic changes in the form of a central chromatolysis, pigmentation, breaking off of processes and eccentric nucleus; the cells have their sides curved outwards. Somewhat similar changes were found in the hypoglossal nuclei of the medulla oblongata. The sixth nucleus appeared to be quite normal. The oculo-motor nucleus was not examined.

The cortex examined by Marchi-Pal method.—There is some diminution of the tangential and super-radial fibres and many recent hæmorrhages into the superficial cortical layers.

The cortex examined by Nissl method shows numbers of small recent hæmorrhages varying from a pin point to a large pin's head in size. They are situated in the superficial layers of the cortex. The vessels show a proliferation of the endothelial nuclei and are mostly dilated and congested with blood (*vide* figs. 1 and 2). The cells are arranged in columns and there is no marked glia cell proliferation, although in the superficial layers there is undoubtedly a considerable increase of neuroglia cells. The ganglion cells show acute changes, probably due to circulatory disturbances, but also some chronic change, for the amount of pigment in the cells is above the normal. Some of the cells besides showing diffuse staining of the body and processes, also show a central chromatolysis and eccentric, swollen, clear nucleus as met with in other cases. The cortical changes are not so marked as in some of the other cases examined.

ON SOME ASPECTS OF THE MENTAL STATE
IN ALCOHOLISM, WITH SPECIAL REFER-
ENCE TO KORSAKOW'S DISEASE.

BY W. L. ASCHERSON, M.D.CANTAB., M.R.C.P.LOND.

Late Medical Registrar, St. George's Hospital.

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PREFACE.

The observations upon which this thesis is founded, are based upon an analysis of 245 cases of alcoholism, admitted to the medical wards of St. George's Hospital during the years 1900 to 1904 inclusive. Among these cases were 38 of Korsakow's disease.

In Table I. will be found an analysis of the clinical features of these 38 cases, and of 85 others collected from the literature, in all of 126 cases.

Tables II. and III. contain a more detailed account of my own 38 cases.

I have also appended full notes of 23 cases, in illustration of the various points which arise in the course of the argument.

I wish to express the deep sense of my gratitude to Dr. Mott, not only for the practical assistance he has given me during the time I acted as his deputy assistant in the laboratory at Claybury in placing his pathological sections at my disposal and in affording me the means of investigating cases of insanity in which alcohol was alleged to be the cause of the patient's mental condition, but also for the many valuable suggestions I have received from the benefit of his wide knowledge and experience of my subject.

My thanks are also due to the physicians of St. George's Hospital for permission to publish the accounts of cases admitted under their care.

INTRODUCTORY REMARKS.

In the degraded condition of the alcoholic we recognise that both the body and the mind are affected. The physi-

cal signs of chronic alcoholism are unmistakeable, but the mental symptoms are less definite, and it is often difficult to say how far the altered mental state of an alcoholic patient is the outcome of his habit, and how far it is attributable to other causes.

In the first instance, the very existence of an alcoholic habit often connotes previous mental infirmity; the patient is perhaps congenitally feeble minded, or possessed of some inherent peculiarity of temperament, or is the subject even of some more definite nervous affection, such as hysteria or epilepsy, which may cloak by its presence mental symptoms more specially due to alcohol itself: indeed, the sole effect of intemperance may be to unmask disabilities of the mind which were hitherto latent. When I was examining selected cases at certain of the London County Asylums, I was much impressed by the large number of those branded "alcoholic" in which alcohol had had evidently little to do with causing the mental symptoms, and possibly the failure to discriminate in any case of alcoholism between what is hereditary and what is the result of alcohol may have given rise to much of the discrepancy which exists in the clinical accounts of different observers.

Secondly, alcoholism often complicates other forms of mental disease, which may lend their own colour to the clinical picture. Foremost among these is general paralysis, which, if not often caused by alcoholism, is, at least, more likely to occur among those who have fallen through intemperance into irregular habits. Not infrequently a lapse from moderation into intemperance is but one symptom of the ethical break-down which marks the early stage of general paralysis. Moreover, alcoholism and general paralysis share many symptoms in common.

But, apart from these considerations, the mental symptoms which result either from a direct action of alcohol upon the structures of the cortex, or of an autointoxication due to the changes wrought by it in other organs, have but little special character, a circumstance which should not occasion surprise when we consider that both alcohol itself and the metabolic poisons to which it gives rise,

being conveyed in the blood stream, have a general rather than a local effect upon the nervous structures : now it is a matter of experience that the nature of nervous symptoms depends more upon the site of a lesion than upon the morbid agent producing it. Broadly speaking, alcohol, whether its action be direct or indirect, may modify the structures of the cortex in two ways ; it may either destroy them outright, or may give rise to certain definite changes in them short of destruction. In the former instance there results clinically a dementia, which differs in no respect from that which is due to other causes ; the latter finds expression clinically in a diminished state of consciousness accompanied, in some cases, by delirium, and to a particular affection of the memory, symptoms which are likewise in no way special to alcoholism, but are common to many other diseases.

There are, however, certain mental symptoms whose presence in a case, if not pathognomonic of alcoholism, afford, in the opinion of some, strong grounds for assuming that alcohol was concerned in the etiology : these are morbid jealousy and suspicion, certain delusions relating to the marital or maternal instincts, terrifying or threatening auditory hallucinations, and a mood which alternates between fearfulness and anxiety on the one hand and gaiety and even jocularly on the other. There are those who refuse to admit that even these symptoms are peculiar to the mental state of alcoholics, but prefer to regard them as merely individual traits of character revealed or accentuated by the alcoholic habit.

In alcoholism then we may encounter :—

(A) Mental affections which are the outcome of either a direct or an indirect action of alcohol upon a hitherto healthy brain : (1) So intense as to lead to destruction of the elements of the cortex and give rise to dementia ; (2) sufficiently intense only to produce changes short of destruction and give rise to (a) a diminished state of consciousness with or without delirium, (b) a particular kind of disturbance of the memory.

(B) Mental affections more especially due to the action

of alcohol upon an abnormal brain, whose symptoms express for the most part accentuated individual and inherited peculiarities.

(C) Other mental affections with which alcoholism is casually associated.

In practice but few cases of alcoholism are encountered in which the mental symptoms fall under one of the above headings to the exclusion of the others, but whereas the alcoholic insanities, properly speaking, the alcoholic paranoia, and the acute alcoholic hallucinatory insanity described by German writers derive a large number of their symptoms from the individual and inherited peculiarities of the patients, such affections as alcoholic dementia and delirium tremens do so very little, and must be regarded more as the effects of alcohol upon a previously healthy mind.

The alcoholic insanities fall rather within the province of the alienist, and I shall allude to them but cursorily in the course of this essay. Two forms of alcoholic mental affection occur frequently in the practice of a general hospital, these are delirium tremens, and a group of mental symptoms which is usually, though not invariably, associated with multiple neuritis.

To this group and the neuritis which accompanies it the name of psycho-polyneuritis has been given, or Korsakow's disease, after the Russian alienist who was the first to describe it. While the disease has led to much discussion on the part of alienists and neurologists abroad, and has formed the subject of a large number of monographs, in England it has so far met with but slight recognition. Korsakow's disease is of interest because its close resemblance to other forms of mental affection often occasions difficulties of diagnosis, and because the study of it leads to the discussion of some important principles of mental disease in general; I have, therefore, decided to make it the chief subject of this essay.

KORSAKOW'S DISEASE.

Synonyms.—(1) Korsakow's syndrome; (2) polyneuritic psychosis; (3) psycho-polyneuritis; (4) cerebropathia psy-

chica toxæmica; (5) dysphrenia alcoholica polyneuritica (Kahlbaum).

I.—HISTORICAL SURVEY.

Though for more than half a century mental symptoms had been observed in connection with various forms of intoxication, and, in the case of alcohol, had been fully described by Magnus Huss as early as 1859, their presence in cases of multiple neuritis does not seem to have been remarked until twenty years later, at a time when neurologists were learning to distinguish that disease from other forms of spinal paralysis. Tiling (1) and, at a later date, Wehrung (2) have collected independently the earlier records of cases; among the symptoms described in these were sluggishness and confusion of mind, disorientation in time and place, loss of memory, visual hallucinations and a loss of the ethical sense of the kind encountered in general paralysis.

It is clear from the accounts of those cases to which I have had personal access that, for the most part, no suspicion of any essential connection between the neuritis and the mental symptoms crossed the minds of the observers. At that time the histological changes in the cord, which are now held partly responsible for neuritis, were as yet undiscovered; the conception of the neurone even was in its infancy and multiple neuritis was considered strictly a disease of the nerve endings themselves. Neurologists, observing that the mental symptoms occurred almost exclusively in connection with alcoholic neuritis, naturally attributed them to an independent action of alcohol upon the brain, a conception which was no doubt borne out by the frequent co-existence of ocular and facial palsies, at that time held to have a central rather than a neuritic origin. Among the few earlier writers who stopped to consider the possibility of a bond existing between the neuritis and the mental symptoms, Fischer (3) refused to commit himself to a definite opinion of its nature and Strumpell (4) positively denied the possibility of its existence. Liliensfeld (5), writing in 1885, seems to

have been the first who admitted an essential relation between the two: in summing up the features of one of his cases he writes: "The psychical symptoms are in no way to be considered as accidental accompaniments, rather as integral features of the disease." But to Korsakow we are indebted not only for the first detailed description of the mental symptoms, but for the first serious attempt to put upon a firm basis the nature of their relation with multiple neuritis. The first publication of this writer appeared in the *Moniteur Russe de la psychiatrie et de la neuropathologie*, under the title of "Trouble mentale dans la paralysie alcoolique, et son rapport avec la dérangement de la sphere psychique dans la névrite d'origine non-alcoolique." Other papers by him followed in Russian periodicals in 1889 and 1890, and in 1889 the whole subject was ventilated at the Paris Medical Congress: subsequently Korsakow published papers in 1890, 1891 and 1892 in German periodicals.

In his first German publication Korsakow (6) definitely enumerated the three cardinal symptoms of his malady:—

- (1) Irritable weak-mindedness.
- (2) Mental confusion showing itself particularly in judgments of time and place.
- (3) A form of amnesia in which the memory for recent events is chiefly affected.

Korsakow considered that these three symptoms together constituted a mental syndrome invariably found in relation with peripheral neuritis, and that the mental symptoms and the neuritis were alike expressions of a toxæmia of the nature of ptomaine poisoning. He was also the first to deny the existence of an essential relationship between the mental symptoms and alcoholism, and brought forward evidence from his own cases to show that they might accompany multiple neuritis due to other causes. Among his non-alcoholic cases were two in which the mental symptoms with neuritis followed uterine sepsis, one in which they followed typhoid fever and one in which they appeared in a case of chronic paludism complicated by lymphadenoma. To the mental syndrome and the neuritis Korsakow gave the name "psychopolyneuritis," and at a

later date substituted that of "cerebropathia psychica toxæmica" as being of more general application in that it served to include cases in which, although mental and other cerebral symptoms were well marked, the neuritis was so slight as to escape superficial observation.

The publications of Korsakow gave rise to much discussion and adverse criticism, chiefly at the hands of French and German alienists, and numerous monographs began to make their appearance, many of which contained accounts of cases. Among the more important of those published in Germany are the articles of Tiling (1890), Jolly (1897), Kahlbaum (1899), Chotzen and Gieser and Pagenstecher (1902), Meyer and Raecke (1903), Bödeker (1904) and Wehrung (1905). The subject has been fully treated by Bonhöffer in his work entitled "Die Akuten Geisteskrankheiten der Gewohnheitstrinker," and by Professor Kraepelin in his recent Textbook of Mental Diseases. In France Korsakow's disease has formed the subject of the Paris theses of Haury and Chancellay and of the Lyons thesis of Carrier, and has received full attention at the hands of Babinski in Charcot and Bouchard's System of Medicine, by Professor Raymond in his lectures delivered at the Salpêtrière, and by Dupré in Gilbert Ballet's recent Treatise on Mental Pathology. The morbid anatomy has been more particularly dealt with by Gudden Raimann and Siefert in Germany, and by Chancellay, Gilbert Ballet and Faure in France: in this country S. Cole has recently published the account of a case with a full description of the morbid anatomical appearances. Two exhaustive articles upon the differential diagnosis have appeared in Belgium—one by Soukhanoff and Bontenko and one by Deronbaix. In England, beyond the publication of Cole of which I have just spoken, the subject seems to have received little notice beyond the few cursory remarks in textbook accounts of multiple neuritis. John Turner, however, in 1903, published the details of twelve cases which occurred in his practice.

The work of recent observers has added considerably to our knowledge of Korsakow's disease, and, indeed, the scope

of the disease itself is now so amplified that many more symptoms are included than those originally described by Korsakow; consequently some difference of opinion has arisen as to what is actually implied by the term "Korsakow's disease." Owing to recent histological research, however, rendered possible by the discovery of Nissl's method of staining, the essential nature of the disease and its relation with other maladies are beginning to emerge from obscurity and to be more thoroughly understood.

Two questions in connection with the subject have afforded ground for dispute.

(1) Does Korsakow's disease necessarily include multiple neuritis?

(2) Is the disease essentially an alcoholic affection?

Soon after the writings of Korsakow appeared, certain observers began to cite cases in which mental symptoms of the kind occurred apart from multiple neuritis, and the opinion became general that the essential relationship between the neuritis and the mental symptoms which he claimed, was without foundation. Korsakow (7) refused to acknowledge that the evidence of these cases interfered with his original contention, and urged that the presence of multiple neuritis would have been detected in them had they been investigated with sufficient care, and, for a long time, the matter rested upon the decision of the criteria necessary to prove the existence of multiple neuritis in a case, criteria which varied considerably according to the opinion of the individual observer. Recent knowledge of morbid anatomy suggests that neuritis may be looked for in any case of Korsakow's disease, and that its absence in certain cases may be accounted for only by the fact that the morbid process has failed to include the neurons of the grey matter of the spinal cord and of the posterior root ganglia, and Korsakow's original contention is thus becoming reinstated.

The second question, namely, whether Korsakow's disease is essentially an alcoholic affection, remains at present undecided: Bonhöffer (8), Meyer and Ræcke (9), and Kraepelin (10) hold that the disease is an alcoholic affection

and is merely a chronic form of delirium tremens. On the contrary, the French and American schools classify the malady among the toxic insanities, such affections as primitive mental confusion, Meynert's amentia and even acute delirious mania. Certain writers, Séglas (11) and Chastin (12), refuse even to admit that Korsakow's disease constitutes a separate entity, but regard the mental syndrome which accompanies multiple neuritis as merely a form of primitive mental confusion.

II.—GENERAL DESCRIPTION OF THE DISEASE.

Whatever opinion we may hold as to the nosology of Korsakow's disease or as to the nature of its relation with other affections, in a typical case the clinical picture is distinct. This is especially true of those cases in which the neuritis is a prominent feature and it may therefore be of advantage to preface the detailed consideration of the individual symptoms by a short general account of cases of this kind.

The patients, then, are usually women of middle age, the subjects of undoubted alcoholic neuritis. The mental state varies somewhat with different degrees of the malady. In mild cases there seems, at first sight, but little amiss with the patients; their mood is placid, even apathetic, and they seem satisfied both with their own condition and with the treatment they are receiving; they are facile even, and seem eager to create a good impression; their replies to questions are ready and to the point, and often betray a dry humour. In spite of this amiable mood however, one will never wait long before witnessing an exhibition of peevishness and irritability, and often the patients are intractable for days together, constantly grumbling and finding fault if they are not actually rude and insulting. The mood also alternates with surprising rapidity. Towards night the patients nearly always become irritable and excitable; sleep is poor and broken, and after the first spell of it there may be so much restlessness as to lead to attempts to get out of bed; at night, too, the conduct and attitude of

the patients suggest that they are suffering from visual hallucinations of an unpleasant nature.

The intellect at first seems unaffected, but a short conversation soon betrays wherein it is lacking. The memory, though certain enough in a general way, and especially for experiences of long ago, is usually defective for much which has occurred in the immediate past; moreover, each new circumstance is forgotten in measure as it is acquired. No feature of the malady is so striking as this, that a patient who has been for some time conversing rationally, will have forgotten, after a short time has elapsed, not only the topic of the conversation but the very fact of a conversation having taken place, and will treat those who shared in it as complete strangers. The patients are very apt to give long accounts of their past experiences, and although their story bears the semblance of truth, a subsequent comparison with the facts derived from other sources may prove that it was false; it is on this account that they are often branded as intentional liars by those who do not realise sufficiently the nature of their malady. Further, in striking contrast to intellectual faculties in other respects unimpaired, the patients often have no idea of the time or place, or even of the identity of persons about them, who they frequently mistake for relatives and old acquaintances.

In cases of moderate severity the abnormal mental state is obvious at a glance; when undisturbed the patients appear to be apathetic and to take but little notice of their surroundings; the attention is with difficulty secured even for a few moments and is extremely fugitive. When attempts are made to rouse them from their lethargy they betray much irritability and look astonished and startled as does a person suddenly aroused from deep sleep. When spoken to they answer incoherently, the train of thought seeming to wander at random from one subject to another; still at times they are able to converse rationally, and then the defect of memory and disorientation are made manifest. At night such patients are delirious; they are extremely restless, fumble in the bed clothes for imaginary objects and

hold conversations with imaginary persons, from the tenor of which it seems as if they were re-enacting some scene of the past; they are also undoubtedly the subjects of visual hallucination: sleep is usually absent, but by the morning the delirium has disappeared and the mood is again one of apathy.

In cases of still greater severity, the condition amounts to one of stupor; the patients lie motionless in bed, oblivious of their surroundings, with the limbs sometimes rigidly flexed or hyper-extended: none but the very strongest stimuli can rouse them into consciousness and then only for a few moments at a time. While in this state urine and fæces may be passed involuntarily. The deep reflexes are usually increased unless abolished by neuritis; the superficial reflexes are nearly always hyper-active.

In all cases the severity of the symptoms varies much from day to day (*cf.* Case 2, Group A) and a patient whose symptoms at one time are confined to a failure of memory and slight confusion of mind, may within a few moments lapse into unconsciousness from which she recovers as suddenly.

Certain mental symptoms of secondary importance are rarely wanting and will be discussed more fully below; some of these, delusions of persecution and auditory hallucinations, features of other forms of alcoholic mental affection, may be of importance in serving to distinguish alcoholic cases of Korsakow's disease from others.

Besides the neuritis certain physical symptoms are encountered in these cases pointing not only to disease of the nervous system, but of other parts of the body, and are of considerable importance. Their presence, as Korsakow (7) has pointed out, serves to show how wide is the distribution of the underlying morbid process; many of them also by their nature add to the difficulties of diagnosis.

I shall consider these physical symptoms separately when I come to discuss the clinical features of the malady more in detail.

III.—ETIOLOGY.

Age.—The average age of the patients in 126 cases of Korsakow's disease was 46 (Table I.) ; that of my total 245 cases of alcoholism, 42·6, whereas that of the 37 cases among the 245 in which delirium tremens occurred in the absence of any other mental affection was only 40·2. These figures favour the contention of Jolly (13), Bonhöffer (8), Kraepelin (10), and Meyer and Raecke (9), who regard Korsakow's malady as a chronic form of delirium tremens, the result of a more long continued habit, and therefore more likely to occur for the first time at a rather later date in the patient's history. My own cases (Tables II. and III.) show a certain disparity between the ages at which either sex is affected; the average age of my men being 49, and that of my women only 39; this disparity concerns those cases alone in which multiple neuritis was present; in these the average age of the men was 52, and that of the women 39, whereas in cases in which neuritis was clinically absent, there was no such disparity. My statistics also show that the malady occurs at an earlier age in women who are the subjects of multiple neuritis than in others. The youngest of my patients was aged 23, and I can find no instance of any younger example in the literature; the oldest of them was a man of 68, but both Korsakow (6), and Jolly (13) have described cases in which the disease occurred at a still more advanced age; it is possible, however, that some of these cases of the disease in very old people were instances of senile dementia or arterio-sclerotic insanity, with which this disease has many features in common.

Sex.—71 (59·5 per cent.) of 126 patients were men and 55 (40·5 per cent.) women. These figures are however scarcely to be relied upon, for the material of some of the series of cases analysed was without doubt derived from members of one or other sex exclusively. In this respect the statistics of my own cases (Tables II. and III.) collected from both sexes impartially are perhaps more trustworthy: in these, 38 in all, 19 of the patients were men and 19 were

women, 50 per cent. of either; of the total 245 cases of alcoholism, 159 (64 per cent.) were of men and 86 (35 per cent.) of women: in Korsakow's disease therefore the proportion of women affected is relatively higher, a fact which is also borne out by the statistics of Jolly (13). This contrasts strikingly with what was found in 37 cases of delirium tremens, only 6 (16 per cent.) of which were of women, a proportion which was also found by Hill Buchan (14) in his 230 cases of delirium tremens.

Multiple neuritis occurred in a large proportion of my female patients (69 per cent.); on the contrary, most of my patients without neuritis (80 per cent.) were men. Such figures only confirm what is a matter of common observation, that the malady occurs in its most typical form among women, in whom it is above all the form of mental affection likely to follow long continued and habitual intemperance.

Incidence.—Excluding readmissions, about 7,000 cases were admitted into the Medical Wards of St. George's Hospital during the years 1900 to 1904 inclusive; among these were 38 of Korsakow's malady, or 0·54 per cent. of the total number. The cases included 245 of pronounced alcoholism, in 173 (70·4 per cent.) of which mental symptoms of some kind were noted. Forty-five (or 18·4 per cent.) had an attack of delirium tremens during their stay in the hospital, and 38 (16·5 per cent.) symptoms of Korsakow's disease; fits of an epileptic nature occurred in 21 (or 8·5 per cent.) and typical symptoms of hysteria in 14 (5·7 per cent.): the mental state of one patient was somewhat akin to the alcoholic paranoia of German writers, but the symptoms were not very pronounced. In the remaining 53 cases the mental symptoms suggested neurasthenia, and not a few of them were mistaken for instances of the primary form of that affection, the existence of their habit apparently having escaped notice.

The influence of heredity.—In Tables I., II. and III., I have stated those few facts, gleaned from the family history of the patients, which might presumably have had an influence upon their ultimately acquiring the malady, but it must be admitted that the evidence I have been able

to collect is far too scanty to be of any statistical value ; indeed, to obtain such evidence from hospital patients is a well nigh impossible task, for not only have their statements the inaccuracy which is usual among the uneducated, but they themselves are further prevented by the very nature of their complaint from giving a reliable history : many of them, too, are vagrants, who have long ceased to hold any communication with other members of their families, and the casual information to be obtained from their friends is valueless. Even if the immediate family history of the patients could be obtained, the evidence afforded by it would be insufficient, for Dr. Mott has informed me that, in his opinion, no history in a mental case is of any value which does not include the collateral branches of the family. It is perhaps for these reasons that this aspect of the subject has received so little attention from other writers.

In 17 of my 38 cases (Tables II. and III.), there was a history of mental or nervous disease in other members of the family. In 2 cases there was a family history of alcoholism, in 4 of insanity, in 3 of epilepsy, and in 5 of other nervous affections ; in 7 of the cases there was a family history of phthisis. The cases of alcoholic epilepsy show even less the influence of heredity ; on the contrary, among the hysterical cases, the proportion with a disposition to nervous disease is relatively greater. On the whole, I am of opinion that Korsakow's malady is a form of mental affection which is rather more prone to occur among alcoholics with a sound mental inheritance. Meyer (15) and Luther (16) have pointed out that the forms of alcoholic mental affection which are influenced by heredity appear usually in a very early stage of alcoholism, sometimes even follow the first serious bout of drinking. Now Korsakow's malady is essentially a late manifestation of alcoholism, and occurs exclusively among those who have preserved their mental faculties intact for many years, in spite of continuous hard drinking, and in whom alcohol has already wrought considerable change in other organs. It would seem as if those hereditarily dis-

posed become insane, and therefore removed from exposure to alcohol, before the stage of alcoholism has been reached at which it is possible for Korsakow's disease to show itself. Further, the subjects of Korsakow's disease are usually free from any stigma of degeneracy; apart from the mental symptoms proper to their malady, they show little eccentricity of character or want of mental balance, and are of a good type both mentally and physically. In the cliniques of asylums, where I have had an opportunity of observing them side by side with the subjects of other forms of alcoholic mental disease, they contrasted strikingly with the degenerate rendered insane prematurely by the casual abuse of alcohol.

Other disposing causes and conditions with which Korsakow's disease is associated.—Despite the evidence adduced by Korsakow to prove that his disease can occur in other connections than alcoholism, it must be admitted that hard drinking has at least a share in the etiology in an overwhelming majority of the cases. A reference to Table I. will show that, excluding my own 38 cases, compiled solely from alcoholic material, alcohol was the recognised cause in no less than 74 of the remaining 88 (84 per cent.), and I am convinced that a more careful investigation of the histories of non-alcoholic cases would only serve to swell the numbers of the alcoholic at their expense. In many an instance it is clear that the attention of those who observed the case has been diverted from evidences of alcoholism afforded by the patient's condition, and has been centred on some prominent event in the history, such as a head injury or an attack of influenza, which they have, somewhat naturally, held responsible for the symptoms. Among Korsakow's own cases (6), for example, of which he gave uterine sepsis and other conditions as the cause, alcoholism could be definitely excluded in only one instance, and in the case of cerebral tumour with symptoms of Korsakow's disease, described by Mönke-möller and Kaplan (17), it is significant that the patient made frequent demands for alcohol during the course of her illness, and that the scene of her delirium and the

subject of her pseudo-reminiscence was invariably the tavern. Whatever other conditions may give rise to Korsakow's disease, my own experience has led me to believe that in typical cases, such as I have attempted to sketch above, alcohol can never be excluded from the etiology.

Of other affections with which the malady is found associated (excluding hepatic and gastro-intestinal disease, themselves symptoms of alcoholism), pulmonary tuberculosis comes next in order of frequency. Dupre (18) has insisted upon the importance of this association, and has placed alcoholism and pulmonary tuberculosis in a class by themselves at the head of his list of etiological factors in virtue of frequency and importance; he is of opinion that a combination of these two affections is of great potency in giving rise to Korsakow's disease, and that the presence of pulmonary tuberculosis in a case increases the gravity of the prognosis. Pulmonary tuberculosis was noted in 13 of the 126 cases (Table I.), and in 12 of these the patients were alcoholics.

There was positive evidence of antecedent syphilis in 11 (8 per cent.) of the cases; this is not a large proportion, but it is, of course, impossible to exclude syphilis definitely in others in which there was no positive history of it. There is, however, not much ground for presuming that syphilis is often a cause of Korsakow's disease; the mental and other nervous affections which attend syphilis are sufficiently well defined, both anatomically and clinically, and Korsakow's disease is not one of them.

A certain number of cases have been cited, in which the disease followed one or other of the acute specific fevers; Korsakow (6) quoted two cases following typhoid fever and one following influenza, and Mönkemöller (19) also held typhoid fever responsible for two of his cases. I have had no personal experience of Korsakow's disease in this connection: it is possible that in the practice of a general hospital those cases which follow influenza may escape notice, because the patients are usually discharged within a day or two after the actual fever has subsided

and before the symptoms have had time to declare themselves, but cases of typhoid fever are usually retained until convalescence is well established; yet I can recall no instance in which the disease was followed by any of the symptoms of Korsakow's malady except a transient loss of memory.

Dupre (18) mentions wasting diseases and profound anæmia in his list of etiological factors. I remember a case of carcinoma of the cardiac end of the stomach in which mental symptoms, like those of Korsakow's disease—loss of memory, confusion of mind and disorientation—were terminal events; also a case in which these symptoms followed profound secondary anæmia; but at the time the patients came under my observation, I was unaware of the significance of these mental symptoms, and attached no special importance to them. As I shall have occasion to point out later, the observation that symptoms of Korsakow's disease may accompany severe anæmia has some bearing on the pathogenesis.

Dr. Mott has recently called my attention to the importance of sepsis as an etiological factor; the majority of the fatal cases which he has seen have been females, with evidence at the autopsy of either endometritis, parametritis and salpingitis or venereal disease. He has also observed the presence of oral sepsis in cases, and concludes that it may have determined the onset of the malady, and one of my own cases (Table II., Case 15) certainly seems to support this view. In three of Korsakow's cases (6) also, the symptoms followed septic absorption from the uterus.

Among affections with which the disease has been linked are cerebral tumour (17) (20) and head injury (21). Other forms of intoxication have been held responsible for its development. Jolly (13) has quoted two cases in which the mental symptoms were a complication in arsenical neuritis, but alcoholism could be positively excluded from neither. Lead poisoning is given as a cause by Dupré (18), and quite recently Nina Rodrigues (22) has published accounts of cases of beri-beri in which the symptoms of Korsakow's disease occurred.

Dupré (18) has suggested that the nature of the mental symptoms may vary with the disease they accompany; he states that the form of the disease associated with lead poisoning is more allied to true dementia, whereas the alcoholic form varies greatly, and may show a prominence of any one symptom. Raymond (23) describes headache, giddiness and symptoms of an hysterical nature as special features of those cases which follow carbon bisulphide poisoning. Korsakow (6) professed to discover in his non-alcoholic cases a greater irritability of mood and an absence of euphoria, while Tiling (1) noted in them less apathy.

Most writers conclude that there is justification for admitting a special alcoholic form of the disease. Among its distinguishing features are mentioned euphoria, the existence of morbid ideas of persecution and marital jealousy, the prevalence of visual hallucinations, especially of animals, and of hallucinations of hearing, taste, touch and common sensibility, the prevalence of a dreamy state, a rather special grade of mental confusion, a loss of the ethical sense and a tendency for the loss of memory to become progressive. Now it would seem from the writings of Meyer (15), Luther (16), Bevan Lewis (24) and others, that these are symptoms of any form of alcoholic mental disease; if, therefore, Korsakow's original conception of the scope and nature of his malady can be accepted, I should feel inclined to urge, not that there are special forms of the malady itself, but that it may complicate many diseases with special symptoms of their own. It is not Korsakow's disease which varies, but rather the conditions with which it is associated.

IV.—SYMPTOMS.

Modes of onset.—In 45 (36 per cent.) of the 126 cases (Table I.) the onset of the symptoms was sudden, and in 34 (27 per cent.) gradual; in my own cases (Tables II. and III.) the proportion of the former mode of onset was still greater (15:6). The greater frequency of a sudden onset is due to the large number of cases which either begin with

delirium tremens or follow an attack of an epileptic nature. The onset is more frequently gradual in those cases in which multiple neuritis is present, though even in these the mental symptoms occasionally follow suddenly upon one or other of the determining causes which I shall mention presently. The mental symptoms may either precede or follow the neuritis, or the two may develop simultaneously; among those cases in which a note of this point was made they succeeded the neuritis in 28 cases, developed with it in 21, and preceded it in only 7. It is not uncommon to find that the neuritis, which was hitherto slight, has suddenly increased in severity after some complication or other and is accompanied by mental symptoms.

Korsakow (6) drew attention to the frequency with which severe and intractable vomiting may be a determining cause, and I find a note of it in 19 (15·1 per cent.) of the cases. The vomiting may be merely an accentuation of the habitual morning pituitus of the alcoholic, but it may be, on the contrary, a recent and independent symptom. In Korsakow's case (6) the vomiting occurred, at first, only after food, but afterwards became incessant and uncontrollable ("hartkneckiges Erbrechen"); in 8 (6·4 per cent.) of the cases it was accompanied by diarrhoea. The immediate appearance of Korsakow's disease after an accident of this kind might suggest an origin from the absorption of poisons from an unhealthy gastro-intestinal tract, but I am more inclined to the view that the gastro-intestinal disturbance and the mental symptoms alike express a sudden increase of the morbid processes which were originally the cause of the neuritis.

Mental shock or strain was immediately responsible for the onset of the symptoms in 14 (11·2 per cent.) of the cases, and recent increase of the habit of intemperance in 7 (5·6 per cent.). Severe hæmorrhage preceded the disease in 5 cases (in two instances of metrorrhagia and in three hæmatemesis). Head injury was the determining cause in the two cases described by Kalberah (21), and two cases have been described respectively by Jolly (13) and Meyer and Ræcke (9) in which the symptoms followed

apoplexy. I am inclined to doubt whether symptoms of this kind occurring after an apoplectic seizure warrant the interpretation given to them by these writers, but should rather consider them evidence of gross and widespread vascular lesions of the brain which sometimes occasion a mental state not unlike that in Korsakow's disease.

In 20 (16·6 per cent.) of the cases the mental symptoms of Korsakow's disease followed immediately an attack of delirium tremens, an observation which supports the view of Bonhöffer (8), Kraepelin (10) and others, and there certainly would seem to be many grounds for thinking that Korsakow's disease and delirium tremens are but different forms of the same affection. Both are essentially late manifestations of alcoholism and seem to demand the presence of extensive change in such organs as the liver and gastrointestinal tract. At any time during the course of a case of Korsakow's disease, but especially at night, symptoms may occur indistinguishable from those of delirium tremens. Though delirium tremens is usually a malady of brief duration and terminated in a few days by a critical sleep, cases are encountered (*cf.* Case 5, Group B) in which, after the delirium has subsided, a state of mental confusion in which the patient is disorientated and paramnesic remains and may persist for several weeks; during this period there may be frequent recurrence of the delirium at night, though the patient is quiet during the day; such cases would certainly seem to represent a transitional state between delirium tremens and Korsakow's disease, and more of them might have been recorded had the after state of delirium tremens been more carefully investigated. Even when delirium tremens is at its height many of the symptoms are identical with those of Korsakow's disease; there is the same tendency on the part of the patients to confabulate, their reminiscences always relating to episodes of their past life, particularly to those concerned with their habitual occupation. Bonhöffer (8) states that the nature of the hallucinations is the same in both conditions, and that the objects presented are always in motion; on the other hand he has pointed out a difference in the nature of

the paramnesia in the two affections; whereas in delirium tremens the story of the patient concerns recent events. In Korsakow's disease it concerns those of the far past; also in the former the loss of memory only covers the period of the delirium and is never retroactive as in the latter.

The frequency with which the mental symptoms of Korsakow's disease follow an epileptiform attack, with or without convulsions, is of great interest because of the very close bonds which unite epilepsy with the mental state in alcoholism. In 15 per cent. of the 126 cases the onset was of an epileptic nature (*cf.* Cases 1, 2, 7, Group B), and in no less than 20 per cent. an epileptiform attack occurred during the course of the malady. In 6 of my 38 cases the disease followed an attack of unconsciousness, and in 2 definite convulsions were noted. In the absence of any history of convulsions, it is not always easy, in actual practice, to satisfy oneself of the exact nature of the attack which precedes these symptoms. Patients are often brought into hospital having been found unconscious in the street; on admission the face may be pallid, the pupils dilated and inactive to light, and urine may have been passed involuntarily; the temperature is often subnormal and the pulse feeble. Urine drawn off by a catheter may contain albumen, but the albuminuria is usually transient; occasional twitchings of the limbs may be observed. After a certain lapse of time the patient regains consciousness sufficiently to react to powerful stimuli, his condition having advanced gradually from one of complete unconsciousness to one of stupor. When the stupor has also disappeared the mental confusion, disorientation, failure of memory and other mental symptoms of Korsakow's disease are disclosed. In one of my cases (Case 2, Group B), after the disappearance of the stupor, there was a short interval in which the mind of the patient was quite clear, but the symptoms of Korsakow's disease thereafter supervened and were still present when he was discharged from the hospital. In none of my own cases with an epileptiform onset could I satisfy myself of the

presence of multiple neuritis, but neuritis was present in two out of the three cases with such an onset described by Jolly (13). In Case 2, Group A, however, in which the multiple neuritis was severe, the patient, shortly after admission, suddenly lost consciousness and remained in an unconscious condition for nearly twenty-four hours, the limbs being held rigidly flexed.

Prodromal symptoms.—In cases in which the onset of the affection is gradual, certain prodromal symptoms may often be observed. A gradual failure of memory was noted in 12·8 per cent. of the cases for some time before the other symptoms appeared, and in the same percentage of cases an ill-defined sense of worthlessness and a lack of initiative. Sleeplessness is mentioned as an early symptom in only 4 per cent. of the cases, but from my own experience I feel sure that it occurs more often. Irritability of mood receives mention in 7·2 per cent., suspiciousness, a suicidal impulse, and aprosexia respectively in 1 per cent.

The neuritis, too, may be preceded by certain vague physical symptoms, such as general lassitude, unsteadiness of gait, and fleeting pain in different situations. Now it is important to recognise that these mental and physical prodroma together constitute a condition which can be, with difficulty, distinguished from primary neurasthenia. The diagnosis is particularly difficult in the case of women, because of their habitual want of candour with regard to their habit, and I could point to more than one instance in which a diagnosis of primary neurasthenia has been made, when the patient in reality was on the threshold of an attack of Korsakow's disease. Ségas (11), in his lectures on mental confusion, alludes to a neurasthenic state preceding the malady; de Fleury (25) professed to be able to distinguish between primary neurasthenia and a secondary neurasthenia of alcoholism and granular kidney by the state of the arterial tension; the former he called "neurasthenia of hypotension," and the latter, "neurasthenia of hypertension." In the case of Korsakow's disease I doubt if such a distinction can be relied upon, because in it the arterial tension is so often low.

Mental symptoms.—There are in Korsakow's disease four symptoms which take precedence of all others in importance. These are :—

- (1) Loss of memory.
- (2) Paramnesia or pseudo-reminiscence.
- (3) Mental confusion.
- (4) Certain peculiarities of the mood.

I shall now proceed to consider these somewhat in detail.

Loss of memory.—I have already stated that while the patients fully recollect the general circumstances of their past, they often forget those which have occurred more recently. The period of time in the immediate past for the circumstances of which the memory is defective varies in individual cases, but usually coincides with that of the patient's illness. So far, the amnesia is anterograde and concerns a period during which not only the power of recollection may have been at fault, but when, by reason of an impaired power of attention, the material for recollection was probably lacking. In many cases the patients also fail to recollect those circumstances which occurred within a period of time antecedent to the onset of their disease; the amnesia is retrograde, and, in this case, since the attention before the disease set in was presumably normal, must depend upon a defective power of recollection alone. Clinical observation shows also that the failure of memory is active; that is to say, that facts continue to be forgotten in measure as they are acquired. To this kind of defect of memory French writers have given the name, "*Amnésie continue*"; it is an important feature of Korsakow's disease and is often present in cases in which the memory is otherwise unaffected. This continual failure of recollection, as I shall call it for the lack of a better term, affects all recent acquisitions; not only do the patients immediately fail to reproduce ordinary test words and combinations of figures, but they entirely forget the faces they have just seen and the actions of everyday life they have just performed.

Jolly (13), Tiling (1), and Wehrung (2) consider that when the amnesia is retrograde the prognosis is more grave, but I fail to see how they can have arrived at this con-

clusion except empirically ; as far as the faculty of recollection is concerned a distinction between retrograde and anterograde amnesia can be one of degree only, and there would seem to be no essential reason why patients whose failure to recollect extends to circumstances before the onset of their malady should not ultimately recover their memory, so long as the loss of it depends upon a mere suspension of function.

Smith (26) observed a want of parallelism in individual cases between the loss of memory for the events of recent periods in the past and the continual failure of immediate reproduction which I have mentioned, and argued from this that the former is due to a failure in assimilation during that period for which the memory was defective ; the grounds for this assumption seem to me insufficient, and they do not in any way serve to explain the retrograde amnesia.

On the whole, I am of the opinion that such terms as "retrograde amnesia" and "anterograde amnesia" are only sources of confusion and unnecessary, since by employing them we are not furthered in the discovery what is after all paramount, namely, how far the defect of memory in Korsakow's disease is due to temporary loss of function and how far it depends upon statical changes from which no recovery is possible.

The memory in an organic disease of the brain such as general paralysis, though at the onset defective from a mere failure to recollect, is ultimately lost because the material basis for recollection is destroyed. When this is so the resulting defect of memory is found to obey the law of Ribot, which states that facts disappear from the memory in the order of their recency of acquisition and consequent instability of association ; the dissolution of memory takes place gradually, the acquisitions of the past disappearing one by one. The material basis of memory also is itself destroyed, and what is past can never again be remembered ; the course of the amnesia is progressive and is merely one instance of a general dissolution of the intellectual faculties. In Korsakow's disease, on the other hand, though in many

cases circumstances are forgotten in the order of the recency with which they were acquired, the defect of memory does not so rigidly conform to the law of Ribot ; instances occur in which the reverse is true, and while the recent events of the patient's past are well recollected, those of a period in his more remote past may be completely obliterated. Moreover, the loss of memory is not nearly so gradual as that which is a symptom of organic disease, and, instead of single facts disappearing from the memory one by one, we observe that the whole contents of some period of the patient's past are obliterated from his mind, while all that befell before that period and after it may be well remembered ; as Chotzen (27) has well expressed it, " we may find little islets of memory in a sea of forgetfulness." But the most important respect in which the loss of memory in Korsakow's disease differs from that in organic disease is in that it is not a progressive symptom ; even after the memory has failed for months it may quite suddenly return. Unlike that of organic disease, the state of memory varies also, not only from day to day but from hour to hour ; a patient in Claybury Asylum volunteered the statement that she would remember perfectly well to-morrow that which she had forgotten at the time when I examined her. It is clear from the very fact that the memory does return that the statical basis of it is not destroyed, and that the fault must lie in the power of recollection itself. This is the opinion held by Professor Raymond (28), who speaks of the disturbance of memory in Korsakow's disease as an amnesia of evocation of the kind which occurs in hysteria. Korsakow and Janet (28) indeed go further, and believe that recollection actually takes place but is not represented in consciousness, and, however much one may feel disposed to criticise their assertion, it is certain that the patients, if suddenly taxed, are unable to recollect circumstances which readily come to their mind spontaneously. To this phenomenon the name of " Gedächtnisstutzigkeit " (memory stammering) has been applied by Adamkiewicz. The variable nature of this failure of recollection and its tendency to disappear entirely also seem to show that, if it be based upon any anatomical

change, that change cannot be a permanent one, and this is borne out, as I shall show later, by the morbid anatomy of the disease.

So far I have discussed the memory defect in Korsakow's disease solely from the side of recollection, but, as elsewhere, the state of the memory does not depend only upon impairment of recollection but also upon a failure of the power to assimilate, or in other words—a failure of attention. It is not always easy to determine how far failure of attention in the past is responsible for the state of the memory in any particular case; in the majority the period for which the memory is deficient coincides roughly with the duration of the illness. Now, even in the mildest cases, the power of attention is much diminished, and this is well shown by the listless and apathetic mood of the patients: in severe cases, especially in the first stage of the disease, the failure of attention may be so great that no external impressions reach consciousness at all. So far it would seem then as if a want of attention were responsible for much of the loss of memory in Korsakow's disease, at least for that which concerns the experiences of the illness itself; yet it sometimes happens that the patients accurately recollect at a subsequent date many circumstances of which, at the time, they appeared to be oblivious. How is this to be explained? I think the assumption is forced upon us that impressions can be received and associations of them made, in some way, outside the full consciousness of the individual and be afterwards at the service of the memory. Again, we are dealing with a failure of power, in this instance the power of attention; the fault is dynamic and not such as could be accounted for by an irreparable statical change.

The memory defect in Korsakow's disease is therefore due to a disturbance of function, namely, a failure to assimilate impressions received from without into consciousness and to represent those before it which have already been assimilated in the past; in other words to a failure in mental synthesis.

It must not be imagined that the disturbance of memory is confined in all cases to this functional dysmnnesia. In a

large number of cases although the memory is recovered to a certain degree, some impairment of it remains permanently, and the residual defect is of the same nature as that which we find in organic affections. This, as I shall also show, coincides with the morbid anatomy of the disease.

I need hardly emphasise the importance of being able to determine how far the loss of memory in any case is merely a disturbance of function and how far it depends upon statical changes from which no recovery is possible.

Paramnesia (Pseudoreminiscence. False memory). Paramnesia, or the representation before consciousness of false experience, is an essential feature of the malady, and though it was recorded in only 70 per cent. of the 126 cases, I have rarely seen an instance of the disease in which it was absent. This symptom has been very carefully studied by Korsakow (29) and has formed the exclusive subject of one of his monographs; Professor Kraepelin (30) and, more recently, Wehrung (2), have also attempted to explain it psychologically. Wehrung (2) divides paramnesia into:—

(1) *Erinnerungsfälschungen* (Illusions of memory).

(2) *Erinnerungstäuschungen* (Hallucinations of memory).

In the former the false representation is suggested by some present circumstance; the patient either sees some object or hears something spoken of which he weaves into the fabric of his own past experience; in the latter, the false memory is not suggested by present circumstances, but is wholly a product of the imagination. Kraepelin (30) has pointed out that there are an infinite number of grades of false reminiscence between "*Erinnerungsfälschungen*" on the one hand and "*Erinnerungstäuschungen*" on the other; he gives as an example of the former that common symptom of fatigue which consists in the belief on the part of the individual that the identical circumstances, of which he is a witness, have occurred at some time in the past, and to this very complete form of illusion he has given the name of "*Identificirenden Erinnerungsfälschungen*"; it corresponds with what is known by French psychologists as "*l'expérience de déjà vu.*" As the "*Erinnerungstäuschung*"

or true hallucination of the memory is approached, the suggestions afforded by the realities of the present gradually make way for the products of the imagination, and the more the paramnesia is of the nature of an hallucination of memory, the deeper is the disturbance of ideation.

Objective evidence of their false reminiscence is afforded by the confabulation of the patients, and it is this symptom which has no doubt given rise to a suspicion of deliberate falsehood on the part of those who do not sufficiently understand the nature of the malady ; it is, however, undoubtedly true that these patients tell lies wilfully, not only for the sake of expediency, but also in order to conceal their defective memory.

The content of the paramnesia yields valuable evidence as to the extent to which the ideation is at fault ; in Korsakow's disease, however fanciful may be the ideas, they are never, as in general paralysis, improbable or absurd ; usually the patient's story is coloured with the details of his professional occupation, and at least concerns experiences which might reasonably have befallen him. Korsakow (29), from an observation of his cases, concluded that the false reminiscence can always be traced to some actual circumstance in the past life of the patients, which, however, may be so distorted as to baffle recognition.

The attempt to explain the psychology of paramnesia has given rise to much conjecture on the part of different writers. Korsakow (29) supposed that, by reason of enfeeblement of mental power, impressions from without, received and stored in the memory, cannot be fully retained ; nevertheless that traces of them remain (*Gedächtnisspuren*) ; the associations formed from these traces of memory, themselves imperfectly made, when again brought before consciousness in a subsequent act of recollection, constitute a false reminiscence. In our present imperfect knowledge of the material basis of mental operations it is difficult to criticise such a view.

I submit in my turn the following provisional explanation of paramnesia. The stimulus afforded by an impression from without alters the constitution of those neurons

which subserve the processes of ideation in such a way that a free communication is opened up for the passage of impulses from one of them to another; thus an association of ideas takes place and a concept is made. If the original stimulus be sufficiently strong, it at the same time incites into action certain higher neurones, whose function is to control and inhibit ideation, and through the control so exercised communications are established only between a certain fixed number of the lower neurones and a limit is placed upon the kind of association formed, but if the original stimulus is not strong enough to rouse the function of these higher neurones there is nothing to guide the impulses along any definite paths, and either too few or too many communications between the lower neurones are opened up. The associations formed are therefore too scanty or too numerous and the ideation faulty. These communications made at the time between the lower neurones constitute paths of least resistance for future mental operations; therefore, when a recollection subsequently takes place it is a false one. Here again, if we may accept this explanation, the fundamental fault is a failure of power, in this instance of power to control or to inhibit the association of ideas.

Mental confusion.—A varying degree of mental confusion is always a symptom at some stage of the malady; in some cases it amounts to positive incoherence, and is then so prominent a feature as to overshadow completely the disturbance of memory. Such cases were recognised by Korsakow, who spoke of the patient's condition as "Apathische Verwirrheit," and they constitute also the "forme confusionnelle" of French writers. Very often the disturbance of the ideation is limited to a disorientation in time and place, with, perhaps, confusion of the identity of persons, and the appearance of these symptoms in an otherwise normally-minded individual produces a very incongruous effect. These isolated symptoms, and in fact mental confusion in general, seem to me to denote a condition of partial stupor. In stupor, the attention is practically in abeyance and no impressions from the outside world reach

consciousness ; nevertheless the mind is occupied with a train of ideas, many of them fanciful and many taking the colour from some circumstance within the past experience of the individual ; the objective expression of these ideas constitutes delirium. Stupor, in fact, would appear to be none other than a condition of pathological sleep of which the delirious ideas are the dreams. With the return of the power of attention, a stage of consciousness is arrived at in which some external impressions force their way into the mind, but are not vivid enough to occupy it entirely or to replace the delirious ideas ; it is as if there were a struggle between the realities of the present and the patient's delirium for mastery in the field of consciousness. This is the degree of consciousness which, to my mind, represents the stage of mental confusion, a stage, if you will, of waking from pathological slumber. Now the judgment of an individual accepts for real whatever is at the time most vividly represented in consciousness ; so long as outside impressions are too feeble to reach it, he is convinced of the truth of his delirium, but as soon as they begin to gain the upper hand and to partially replace the delirious ideas, he accepts for the truth a mixture composed of proportions of reality and delirium varying in measure as one or other is more vividly represented ; the irreconcilable nature of this mixture gives rise to the astonishment which his countenance very well betrays, and indeed the facial expression in mental confusion (the "facies ahuri" of Séglas) (11) is much like that of a person incompletely roused from deep slumber. There is however this distinction between normal sleep and stupor ; whereas in the former the stage of waking occupies but a few moments, in the latter it may persist indefinitely ; nevertheless at times the act of waking even from normal sleep may not be so sudden but that the individual has time to realise his confusion, and the sensation of being momentarily disorientated after sleep is within the experience of most of us. As present realities gain more and more of the field of consciousness, a stage is reached in which but a few isolated delirious ideas persist ; experience shows that, in Korsakow's disease, these are

concerned with impressions of time and place and of the identity of persons. In practice we find that the patient's interpretation of time and place is always made to fit some scene of his past life, a scene usually connected with the performance of his professional duties, and that persons present are mistaken for those who took a part in it: now it is just such a scene which in these cases forms the content of the delirium.

The mood of the patients.—Unless frequent attempts are made to engage their attention, the patients are more or less oblivious to surrounding circumstances, and this occasions the condition of apathy to which their dull and listless facial expression bears witness. When roused, they are wont to be extremely irritable, and this I attribute, in part, to the recognition of their confused state of mind, although it is no doubt due to some extent to a primary instability of the emotions. Mention is made of an euphoric mood in as many as 40 (32·6 per cent.) of the 126 cases (Table I.), and a jocular tendency was noted in 15 (12 per cent.). Euphoria, in my experience, is a special quality of mild and convalescent cases; it is also, when combined with jocularity, a feature of the mental state of alcoholics in general, and is the more striking because of the misery with which these patients are so often afflicted. Such a mood may be perhaps accounted for by the freedom of ethical responsibility which the moral degradation of the patients implies, for I have often observed an uncontrollable tendency to joke on the part of those who are either incapable of realising serious responsibility or who persistently shirk it.

A mood of fearfulness and anxiety is mentioned in 9·6 per cent. of the cases; this may to some extent arise from the terrifying nature of the visual hallucinations.

Bevan Lewis (24) has remarked upon the rude and impulsive conduct of the patients. While such conduct may be in part an instance of moral degradation, it has, in my opinion, a deeper significance. Rudeness and impulsiveness is very often a symptom of epilepsy and dementia præcox; in common with imitateness, attitudinising,

echolalia, the use of neologisms and other forms of automatism, it is an instance of katatonia, or the undue expression of low forms of mental activity insufficiently controlled by higher mental faculties, and is but another instance of an incomplete state of the consciousness.

The patients are often emotional, but their emotions are never profound, and the same may be said of their depression, which is rarely more than skin deep. In fact, whatever be their mood it never persists for long, but is continually changing, and indeed must be regarded as the accompaniment of a dream state rather than as a part of their true nature; in further proof of this is the excitability, which is always greater at night, at a time when the further removal of consciousness by approaching sleep gives freer sway to delirium.

Certain subsidiary mental symptoms have now to be considered which, though they find a place in all more recent accounts of cases, were not a part of the mental syndrome originally described by Korsakow. These are: visual and auditory hallucinations, hallucinations relating to other senses, and certain delusions.

Hallucinations.—Visual hallucinations were noted in 23 (18·2 per cent.) of the cases (Table I.), aural hallucinations in only 5, the reverse of what obtains in cases of acute alcoholic insanity, where the latter are more usual (E. Meyer (15), Bonhöffer (8), Luther (16)). This is important from the point of view of etiology, since visual hallucinations are the kind most often encountered in the delirium of the acute specific fevers and in the toxic insanities. Zoopsia is mentioned as a symptom of 11 cases. According to Bonhöffer (8) zoopsia is not, as was formerly thought, confined to delirium tremens and Korsakow's disease; he considers that a much more constant character of the visual hallucinations in these affections is the constant movement of the objects presented to the patient's vision, which he attributes to a disturbance of the oculomotor function. The visual hallucinations in Korsakow's disease are also not isolated as in some forms of insanity, but represent a continuous scene: to hallucinations of

this kind Bonhöffer (8) has given the name "pseudo-hallucinations"; he looks upon them as merely a part of the delirium of the patients, which disappear upon the complete return of consciousness, in distinction to true hallucinations which occur when consciousness is fully present; for this reason also the visual hallucinations make no lasting impression on the mind of the patients, and in no way permanently influence their conduct.

The aural hallucinations in Korsakow's disease are of a terrifying nature; the voices seem either to threaten the patients or to cast aspersions upon them, usually of an obscene nature. Unlike the visual hallucinations, they are not altogether a part of the delirium, but persist in full consciousness, and are therefore of graver prognosis.

Tactile hallucinations were present in one of Cole's cases (31) and also in one of my own (Case 2, Group A). In Cole's case the patient experienced a feeling as if her hands were encased in tight-fitting gloves; my own patient complained that her fingers were anointed with sticky material, and that gristle kept slipping through her fingers. In both these cases the multiple neuritis was severe and affected the upper extremities as well as the lower, and I am therefore inclined to think that the symptom was based upon morbid sensations conveyed from the periphery and was more of an illusion than an hallucination. Hallucinations of taste occur in not a few cases, and when present sometimes give rise to the morbid idea that the patient's food has been poisoned.

Delusions.—Delusions were noted in a certain proportion of the cases (Table I), and Mönkemöller (19) regards them as an essential to the mental state in Korsakow's disease. Morbid ideas of persecution occurred in 21 cases (16·8 per cent.), and are undoubtedly the form of delusion usually encountered; that their food is being poisoned, or that their neighbours are attempting to rob them, form continual themes for the accusations of these patients.

The frequency of morbid ideas relating to the sexual function, including the marital and maternal instincts, has been emphasised by John Turner (32): in four of his twelve

cases the patients imagined infants were in bed with them, and I noted the same delusion in two of my cases (Cases 2 and 4, Group A). Dr. Jones of Claybury has informed me that in his opinion this particular delusion is so typical of alcoholism that its existence always confirms his suspicions of its presence in a doubtful case.

The patients are often morbidly jealous, and when married, their jealousy may give rise to suspicions of infidelity on the part of their husbands (Case 5, Group A).

Delusions of grandeur were mentioned in five of the cases, and some writers consider that their existence is an indication of dementia and influences the prognosis unfavourably. I do not consider that such an assumption is warranted; grandiose ideas may occur in any mental affection in which there is exaltation, and from some of these, as, for instance, manic-depressive insanity, recovery is possible; the existence of ideas of grandeur in a case of Korsakow's disease has sometimes led to an erroneous diagnosis of general paralysis.

The delusions, whatever be their nature, share the unreal character of the hallucinations, and are more a part of the delirium than ideas formed in the presence of full consciousness; for this reason they rarely become systematised, and, unlike the acute forms of alcoholic mental affections, Korsakow's disease does not often lead to chronic delusional insanity.

Conduct of the patients.—Apart from occasional rudeness and impulsiveness, there is certainly nothing in the conduct of these patients to justify their being certified as insane; among the poorer classes many of them find their way into asylums on the score of incoherence or loss of memory, but when these symptoms subside, as they very speedily do under suitable treatment, the behaviour of the patients is rational enough. The patients are, as a rule, keenly alive to their mental shortcomings, and make use of devices to obviate the consequences which may arise from them.

Faulty habits were noted in 21 (16·8 per cent.) of the cases; it is important to realise that these usually occur when the state of the consciousness is much diminished,

that they are then merely due to inattention and are by no means a proof of the existence of dementia. In those few cases, however, in which uncleanly personal habits persist in a state of full consciousness dementia may exist and render the prognosis more grave.

Recapitulation of the mental symptoms.—In the foregoing pages enough has been said to indicate the defect which lies at the root of the mental symptoms of Korsakow's disease: it is a failure in the power of mental synthesis, and of it the two fundamental symptoms of the malady, the aprosexia and the loss of memory, are but different expressions. When the failure of attention is absolute the patients are impervious to all impressions from without, and their condition is one of stupor; while in this state, however, consciousness is not entirely absent, but the mind may be occupied by a train of delirious ideas, and it is the mingling of these ideas with the realities of the outside world gradually forcing their way into consciousness, which causes the mental confusion. The anomalies of mood as well as most of the subsidiary symptoms, the hallucinations and the delusions depend, as we have seen, upon the delirium, and are not concerned with the conscious ideation of the patient; they are, therefore, evanescent, and leave no permanent impression behind them. The variable degree of intensity of these symptoms and their proneness to disappear entirely are sufficient proof that they are mere disorders of function, and that they do not signify irreparable change within the nervous system.

Physical symptoms.—Korsakow laid great stress upon the fact that his disease was not merely a mental affection, but one of the entire nervous system, indeed, of the body in general, and although the individual lesions are very different from those of general paralysis, the universal nature of their distribution in Korsakow's disease is only equalled in that malady. These physical symptoms are of great importance, especially from the point of view of diagnosis, and it will be, therefore, necessary to consider them somewhat fully.

For convenience I shall divide them into—

(1) Symptoms referable to disease of other parts of the nervous system.

(2) Symptoms of a more general nature.

Symptoms referable to disease of other parts of the nervous system. Multiple neuritis.—There were well marked symptoms of multiple neuritis in 61 (48·4 per cent.) of the 126 cases, and symptoms which justified an assumption of its existence in 39 (30·9 per cent.); in 26 (20·6 per cent.) neuritis was clinically absent.

Korsakow's criteria for the presence of neuritis in a doubtful case, deep tenderness of the muscles of the extremities and slight weakness of the extensors, are perhaps hardly sufficient; on the other hand, those of Jolly (13) are possibly too exacting; in the opinion of this writer a diagnosis of neuritis is only warranted by the presence of considerable wasting and loss of tone of the muscles of the lower extremities, a definitely increased knee jerk and an increase of cutaneous sensibility. I myself should hesitate before making a diagnosis of neuritis upon the evidence of deep muscular tenderness alone; such a symptom is purely subjective, and its significance is much diminished in the case of neurotic patients. The determination of a slight degree of extensor weakness, unless it can be tested by instruments of precision, is open to individual errors of observation. On the other hand, I do not consider the state of the knee jerk a reliable diagnostic criterion in a doubtful case. The tone of the quadriceps extensor is influenced not only by the condition of the lower motor neurons, but by the sensory half of the spinal reflex arc as well as by the neurons of the pyramidal system; these latter influences are antagonistic, and unless the lower motor neurons are destroyed, the supremacy of one or other of them will determine whether the knee jerk is exaggerated or diminished, or, indeed, of normal extent. The truth of this assertion is well shown by those cases of *tabes dorsalis* in which, after an attack of hemiplegia, the knee jerk returns on the affected side. There is, however, some truth in the assertion of Korsakow (6) that neuritis of slight degree may easily escape observation; this is especially so

during the stage of its development, and Korsakow has justly pointed out that, when neuritis follows the acute specific fevers, the slight ataxia, the easily induced fatigue, the vague pains and muscular cramp which are its premonitory symptoms, have been mistaken for the weakness of convalescence. Before definitely asserting that neuritis is absent in any case, it is well to bear in mind that both Jolly (13) and Turner have found changes in the peripheral nerves after death in cases in which there were no symptoms of neuritis during life.

I have usually found that in cases in which the mental symptoms are intense, if neuritis be present at all it is severe, and this is only what we should expect if both have the same origin; the converse, however, does not hold, and cases of severe multiple neuritis are often encountered in which mental symptoms are ill-defined or absent: this is, I think, explained by the readiness with which the mental symptoms respond to treatment, or, in the case of alcoholism, subside when the habit is relinquished, circumstances which render it less likely that they are present at the time when the cases first come under observation.

Cranial nerve symptoms.—Symptoms pointing to affection of the cranial nerves have been described by most of the earlier writers on alcoholic paralysis, but, until recently, their presence in a mental disease of any kind has generally afforded strong grounds for a diagnosis of general paralysis. More thorough observation has shown that they are rarely absent in Korsakow's disease.

Sluggishness of the pupil to light was noted in 19 of the cases and was the most frequent symptom, in 6 one or other of the pupils was inactive to light and the pupils were unequal in 13. The special feature of the pupillary disturbance is that it is transitory and varies much in intensity from day to day; a constant Argyll-Robertson pupil is, in my opinion, never found, and should always lead to a suspicion of tabes dorsalis or general paralysis. I have quoted a case below (Case 3, Group E) in which the diagnosis rested between tabes dorsalis and a tabetic form of neuritis and was finally decided in favour of the former upon the

evidence afforded by the state of the pupil; mental symptoms were present but were not pronounced. The condition of the reflex to light and accommodation varied in this case so much from time to time as to lead to much dispute between independent observers; but by this variable state of the pupil alone I am now convinced that the case was really one of neuritis and not of *tabes dorsalis*.

Ptosis occurred in several of the cases and nystagmus was noted in seven; both these symptoms were transient. Kahlbaum (33) described a whitening of the temporal side of the optic disc in one of his cases, which he considers an appearance peculiar to neuritis; I have no personal experience of this symptom. In all cases in which the mental state of the patients permitted, I tested the range of the visual fields; but in no case which I examined was there concentric contraction of the fields of vision; the absence of this symptom serves as a distinction between Korsakow's disease and hysteria, which it closely resembles in many other respects. I noted dyschromotopsia in one case, but never the central scotoma which has been so often described as a symptom of alcoholism.

Some degree of facial paralysis is almost always present; it is often confined to an obliteration of the naso-labial folds and accounts in part for the stolid facial expression of the patients. Among symptoms pointing to affection of the tenth pair of nerves both Meyer and Raecke (9) and Kahlbaum (33) have alluded to a difficulty in swallowing in some of their cases; this symptom I have never encountered. On the other hand I am convinced of the frequency with which cardiac neuritis is present; in 24 of my own 38 cases (Tables II. and III.) the action of the heart was very feeble and the pulse counted over 110; an irregular and intermittent action of the heart was noted in two cases and an embryo-cardial rhythm in one. Fatty change in the myocardium may have been responsible for some of these symptoms, but the sounds of the heart were far too like those which, in diphtheria, point to implication of the vagus nerve to suggest that it was so entirely. Diaphragmatic paralysis was the cause of death in two

cases. The significance of symptoms such as cardiac failure and dyspnoea is obvious when the multiple neuritis is severe and affects the nerves of the extremities also, but is apt to escape recognition in cases in which the mental symptoms alone are prominent. In any case of mental affection of this nature the presence of an unaccountable feebleness of the heart's action with a persistently rapid or irregular pulse, should certainly favour a diagnosis of Korsakow's disease.

Disturbances of speech.—Aphasia is much more common than would appear from the statistics in Table I.; it is probable that this symptom has been only recorded when it was a prominent feature of the malady, but, as might be expected, both the motor and sensory kinæsthetic functions are often affected with the rest of the memory. Motor aphasia was recorded in five of the cases and sensory in four; but, as is usual when aphasia is a symptom of a morbid process of general distribution, it is not confined to one of the functions of speech only; thus in Korsakow's disease, the motor aphasia is usually complicated by paraphasia. Freund (35) has described an amnesic agraphia which occurs only in severe cases and is of bad prognosis. The aphasia, like the other mental symptoms of the disease, is purely transient and differs only from that of hysteria in developing and disappearing less suddenly and being less complete (compare Case 2, Group A, with Case 1, Group B). The disturbance of articulation is important because, when combined with paraphasia, it constitutes a speech defect not unlike that of general paralysis. Bödeker (20) has called attention to an affection of the speech which is perhaps peculiar to Korsakow's disease; in the course of speaking the patient suddenly pauses on some syllable which he continually repeats and then becomes silent. This symptom is, I think, but an instance of the automatism to which I have before alluded, permitted by a temporary diminution of consciousness, and is an illustration of the difficulty which these patients experience in maintaining their attention for any length of time.

Tremor.—According to my statistics (Table I.) tremor

most often affects the tongue and was noted in 25 of the cases. Tremor of the hands was mentioned in twenty-two cases, but of the facial muscles in only 3. I am, however, convinced that tremor is equally common in all three: the individual movements are rapid and the range is small.

Physical symptoms of a general nature.—Among symptoms of a general nature Korsakow (7) mentions debility, emaciation, anæmia, headache, vomiting and diarrhœa, certain qualitative changes in the urine and suppression of the menstrual function. I have given full consideration to these general symptoms of the disease in my own cases and an account of them will be found in Tables II. and III. I find that a deterioration of general health amounting to cachexia is commonly present in severe cases, and that even the mild cases are not always exempt from some degree of it. Of my thirty-eight patients, the general health could only be called good in thirteen; weakness was especially noted in six and an extreme degree of emaciation in five; anæmia was present in ten and the condition of eight justified the term "cachexia."

The physical constitution of the patients often deteriorates rapidly, and those who were strong and well nourished at the onset of the disease may become after a few weeks emaciated and bedridden. In very severe cases the general condition is not unlike that of patients in the last stage of some chronic wasting disease—the emaciation is extreme, the skin feels harsh, the tongue is dry and glazed, and the weakness and prostration so extreme that the patients have not even sufficient strength to raise themselves into a sitting posture.

I have already alluded to the feebleness of the heart's action when speaking of the multiple neuritis; even in the mildest cases the arterial tension is low and the pulse rate persistently more frequent than in health.

The condition of the lungs calls for no special comment; signs of pulmonary tuberculosis are encountered in not a few of the cases and the condition of the heart may give rise to bronchitis, and when grave, to pulmonary œdema.

The frequency of vomiting and diarrhœa as a determin-

ing cause of the disease has already been mentioned ; the condition of the gastro-intestinal tract, together with that of the liver and kidneys, have an important bearing on the pathogenesis, and will be fully discussed when I deal with that part of the subject ; but mention may be made here of the observation of Dr. Mott that an advanced grade of cirrhosis of the liver is seldom met with in cases of Korsakow's disease, though the liver is sometimes considerably enlarged, smooth and firm to the touch and anatomically shows considerable fatty change and an early stage of multilobular cirrhosis.

Albuminuria was noted in 12 per cent. of the cases ; it is often a transient symptom and the quantity of albumen is usually small. The urine is sometimes concentrated and deposits lithates on cooling, but the peculiar orange tint described by French writers I observed in only two of my cases.

V.—MORBID ANATOMY.

By reason of the infrequency with which uncomplicated cases come to autopsy but few opportunities occur for studying the exact nature and extent of the histological changes which underlie the mental symptoms in Korsakow's disease.

Wehrung (2) has collected from the literature an account of the morbid anatomy of 34 cases of Korsakow's disease ; the thickening of the pia-arachnoid, the changes in the intima and the adventitia of vessels, the foci of hæmorrhage and softening which are described in some of these cases, make it probable that, before death ensued, the condition of many of the patients had advanced to a stage of dementia, for it is extremely improbable that severe and extensive lesions of this kind can have been responsible for mental symptoms of so transient a nature as those of Korsakow's disease alone. By the employment of Nissl's method of staining certain finer changes in the cells and fibres of the cerebral cortex have been demonstrated which, if not special to Korsakow's disease, were present in all cases in which a microscopical investigation of the cortex, with the aid of recent methods of staining, has been possible and were

the only lesions found by S. Cole (31) (36) in a case which, during life, presented the symptoms of the disease without any complication. Similar changes have been described by a large number of other writers, in particular by Gilbert Ballet (37) and his pupils, Babinski (38) and Chancellay (39), and I have recently had an opportunity of studying them myself in some sections prepared at the Claybury laboratory.

Changes in the cortical cells.—In an uncomplicated case sections of the cortex stained by Nissl's method and examined under a low power of the microscope present an almost normal appearance. The columns of Meynert are well preserved, and there is none of that confusion of the arrangement of the cell layers which one sees in sections of the cortex in general paralysis. There is also no evidence of new capillary formation nor of lymphocyte or plasma cell infiltration of the perivascular spaces or the soft membranes. Under a higher power a variable number of the cortical cells may have an altered appearance; in the sections I examined the change affected to some extent the large and small pyramidal cells; the large Betz cells in cases of prolonged polyneuritis, I am informed by Dr. Mott, invariably show the changes which he has described and figured, viz., disappearance of the Nissl granules except at the periphery of the cell, swelling of the cell and eccentric displacement of the nucleus, which is generally large and clear; often the dendrons appear to be broken off. This agrees with the cases observed by Wehrung, where the change fell principally on the Betz cells. In those cells which are only slightly affected the Nissl bodies are still preserved, but those in the region of the nucleus are rather smaller than normal. The nucleus may be swollen, but is centrally placed; the nucleoli are well defined and the nuclear membrane is intact. In more advanced stages the cells have assumed a globular form and seem to have lost some of their processes; the Nissl bodies have disappeared from the central part of the cell but are still seen at the periphery and at the roots of the dendrites; the nucleus is placed laterally, at the periphery of the cell, and is still apparently intact, but in

a still more advanced stage of the morbid process may be even partially extruded from the cell; its membrane is then broken and presents a crumpled appearance and the nucleoli have disappeared. Here and there plasma cells (neurophages) are seen embedded in the peripheral part of a cell as if engaged in eating their way into its substance. The apical processes of the cells are sometimes shrunk and coiled up in a spiral as if they had been detached from their peripheral connections. None of the so-called sausage cells (Wurst Zellen) described by Alzheimer (40), or other endothelial elements which mark the beginnings of new capillary formation, are to be seen.

Dr. Mott informs me that many of the changes above described do not necessarily denote degeneration or destruction of the neurons, but functional depression. Similar swelling and chromolytic changes he has observed in experimental anæmia, and, so long as the nucleus remains intact a return to normal conditions is possible; but, if once the nucleus is extruded from the cell so far as to cause rupture of its membrane and escape of the nucleoli, then true degenerative changes set in and the cell is destroyed (*vide* "Cerebral Lesions in Psychosis of Toxic Origin," p. 353).

It is impossible to over-estimate the importance of the suggestion afforded by such an explanation of the appearances in the cells; if it be the true one, we are brought face to face with one of the anatomical boundaries between functional and organic disease of the brain.

Enough has been said of the nature of Korsakow's disease to show how well these histological appearances correspond with its clinical aspects and explain why the malady may be recovered from in the majority of instances, but is in others the first step towards incurable dementia.

Changes in the cortical fibres.—According to German writers changes in the nerve fibres of the cortex are the earliest and most essential lesions of the malady. Gudden (41) has described an atrophy of the tangential fibres in four cases, but less extensive than that encountered in general paralysis; the atrophy concerned chiefly the frontal convolutions.

Chancellay (39) has also described this lesion, and considered it the anatomical basis of Korsakow's syndrome in a case of cerebral tumour. Siefert (42) noted fatty degeneration of the fibres of the tangential and supra-radial bundles. Dr. Mott assures me that these cortical fibres cannot be renewed in the same way as the peripheral nerves, possibly because these, like other fibres in the brain and spinal cord, are not provided with a sheath of Schwann. The atrophy of the tangential fibres then might conceivably account for the slight degree of dementia which persists in Korsakow's disease, unless we admit that it is possible for their function to be taken over by fibres as yet uninjured.

In spite of the suggestions afforded by anatomical evidence, it is yet by no means certain how far these changes are to be held responsible for the symptoms of Korsakow's disease. Dr. Mott does not consider the visible histological changes of the cortex in polyneuritic psychosis explain the mental symptoms. Dupré (18) has expressed an opinion that there is no correlation between the mental symptoms of the disease and its morbid anatomy, and cases were observed in Ballet's clinique in which no histological change was detected in the cortex in the face of well-marked symptoms during life. This fact led Ballet and Faure (37) to conclude that some of the cases are of a purely functional nature. Dr. Mott has, however, pointed out that the integrative action of the nervous system depends not only upon the recognisable microscopic anatomical fibrillary *continuum* of the neurons but also upon the physiological synopsis of neuron with neuron, changes in which by present methods are unrecognisable.

The changes just described have also been found in the neurons of the grey matter of the cord and of the posterior root ganglia; they are the basis of the multiple neuritis, and indeed were recognised as such for a long time before any anatomical connection between multiple neuritis and Korsakow's disease was suspected. In Cole's case (31) the change was more advanced in the cells of the cervical and lumbar enlargements than else-

where, and none of the anterior cornual cells escaped in those regions except those of the antero-median group; the cells of the posterior root ganglia were also affected. In the tracts of the cord there was scattered degeneration of the posterior columns of a distribution suggesting that the exogenous fibres were chiefly affected, and some degenerated fibres were also observed in the crossed and direct pyramidal tracts.

In view of the frequency with which cranial nerve symptoms occur, systematic examination of the cells and tracts of the mid-brain, pons varolii and medulla oblongata should yield important results. Such investigations are now being carried out by Dr. Mott at Claybury, but his observations are as yet unpublished. In Cole's case (31) there were changes of the nature of those described in the cortical cells, in the ganglion cells of the nuclei of origin of the third, fourth and sixth pair of nerves; the cells of Deiters' nucleus was affected and those of the nucleus gracilis considerably so; the large cells situated near the median raphe also were affected.

The researches of Raimann (43) and Bödeker (20) have suggested that a connection exists between Korsakow's malady and polio-encephalitis superior hæmorrhagica. These observers have found minute hæmorrhages in the grey matter of the aqueduct and elsewhere in the mid-brain; Dr. Mott also informs me that he has found small hæmorrhages in the cortex.

VI.—PATHOGENESIS.

When speaking of the condition with which Korsakow's disease is associated, I alluded to the overwhelming proportion of cases in which alcoholism is concerned in the etiology; I proffered the opinion that typical cases were never encountered in any other connection and mentioned the view of those who hold that the malady is as peculiar to alcoholism as delirium tremens, of which it might be regarded as a chronic form. On the other hand, not only do these mental symptoms never occur in a large number

of cases of chronic alcoholism, including those of long standing and in which there is neuritis, but, as certain of the cases described by Korsakow and others show, they may follow other affections such as acute specific fevers or sepsis, or may attend the cachectic state of cancer and of other wasting diseases.

Clearly then, Korsakow's disease cannot be due to the direct action of alcohol upon the nervous centres but must be referable to some quality of chronic alcoholism which it shares with other affections, though the preponderance of alcoholic cases would suggest that this quality is perhaps most often one of alcoholism. The condition to which alcoholism leads more than any other malady is disease of the liver, and, in the opinion of the French school, the symptoms of Korsakow's disease are to be ascribed to an auto-intoxication arising from hepatic inadequacy, especially when the excretory function of the kidney is also interfered with. This supposition was advanced by Ballet (44), who pointed out the analogy between the symptoms of the disease and those which occur in other forms of destructive disease of the liver, such as acute yellow atrophy and phosphorus poisoning. Ballet is of opinion that, in the absence of any macroscopical evidence of disease, sufficient fatty change may exist in the cells of the liver to account for hepatic inadequacy and to give rise to mental symptoms. Dupré (18) also holds this view, and states that the intensity both of the neuritis and the mental symptoms varies with the degree of hepatic inadequacy present, which can be estimated by the condition of the blood and the urine; in proof of this assertion he quotes the experiments of Leopold Levi (45). This observer found a peculiar orange colouration of the urine in Korsakow's disease which he ascribed to an excess of urobilin, and he estimated the altered state of the hepatic function in terms of urobilinuria. Korsakow himself believed the disease was caused by the action of noxious substances in the blood of the nature of Bouchard's poisons, and did not think that hepatic inadequacy in itself was able to give rise to the mental symptoms unless the kidneys also were affected.

The foregoing views as to the etiology of Korsakow's

disease should, I think, be accepted with extreme caution. I have made a note of the condition of the liver and kidneys, as far as was possible, in each of my 245 cases of alcoholism. Of the 38 cases in which there were symptoms of Korsakow's disease (Tables II. and III.) clinical evidence of affection of the liver was noted in 23 (64.5 per cent.) and of definite cirrhosis in 6 (16 per cent.). The kidneys were sufficiently affected to cause albuminuria in 11 of the cases (20 per cent.), but erysipelas was a complication in two of these and the albuminuria cleared up as soon as the fever disappeared. Symptoms pointing to affection of both the liver and kidneys were present in only 6 cases (16 per cent.). Of the 5 cases which came to autopsy the liver was cirrhotic in 2, fatty in 2, and normal, macroscopically, in 1; the kidneys were fatty and cloudy in 1 case, granular in 1, and healthy in 3. Among the total 245 cases of alcoholism there was clinical evidence of disease of the liver in 133 (50 per cent.) and albuminuria was present in 76 out of the 222 cases in which a note was made of the condition of the urine. Of the 37 cases of delirium tremens the liver was diseased in 18 (50 per cent.), albuminuria was present in 16 (48 per cent.); both liver and kidneys showed signs of disease in 8 (21.8 per cent.). Among the cases of alcoholism in which there were no mental symptoms during the patient's stay in hospital, signs of disease of the liver were present in 67 per cent. and of definite cirrhosis in 46 per cent., albuminuria was present in 34 per cent., and both albuminuria and disease of the liver in 23 per cent. From the evidence afforded by these statistics then, though disease of the liver occurs in about the same proportion of those cases of alcoholism with Korsakow's disease as those in which there are no mental symptoms, disease of both liver and kidneys is present in a higher percentage of the latter. The statistics also amply testify to the accuracy of Dr. Mott's observation that an extreme grade of cirrhosis is much less common in cases of alcoholism in which there are mental symptoms than in those in which no such symptoms occur.

Whether the contention of Ballet (44) that hepatic

inadequacy sufficient to give rise to mental symptoms may exist in the absence of macroscopical changes in the liver, I am not in a position to judge, but I have recently been informed of a case of Korsakow's disease in which, after death, the liver was found to be normal both macroscopically and microscopically and in which the kidneys were but slightly diseased.

I am not inclined to attach much importance to an estimation of the degree of hepatic inadequacy based upon the amount of urobilin in the urine; Herter (46) gives constipation as by far the most frequent cause of urobilinuria, and considers it improbable that this symptom is ever the immediate result of changes in the liver itself; an orange colouration of the urine also was noted in only 5 of the 245 cases of alcoholism and in 3 of these there were no mental symptoms. I therefore conclude that, though auto-intoxication arising from a morbid state of the liver and kidneys may be in part responsible for the symptoms of Korsakow's disease, they are not entirely so and that an additional cause must be sought for.

Habitual indulgence in alcohol leads to permanent change in the walls of the gastro-intestinal tract, particularly in the stomach, and from the comparatively large number of cases in which an aggravation of symptoms relating to such changes immediately precedes the onset of Korsakow's disease it is possible that gastro-intestinal derangement may be occasionally responsible for the malady. Wehrung (2) alludes to a morbid condition of the intestinal tract as a cause of the disease, and Dr. Mott informs me that he considers it important to study the histological appearances of the gastric mucosa and the chemistry of the gastric functions in all cases. Until such research has been undertaken, this aspect of the pathogenesis must remain undecided.

Wehrung (2), who shared the opinion of most writers that the mental symptoms of Korsakow's disease cannot be ascribed to the direct action of alcohol upon the elements of the cortex, has advanced the hypothesis that they are produced by an antitoxin, gradually formed in the blood

as the result of long-continued dosage with alcohol. In support of this view he states that the mental symptoms do not follow a bout of drinking immediately, but after a certain interval of time has elapsed; by the extra dosage of alcohol the tissues are stimulated so as to produce the anti-body in a quantity in excess of that required to neutralise the alcohol itself; the process of neutralisation occupies the period of time immediately succeeding the drinking bout, and after it is finished the excess of antitoxin can exert its own influence upon the cortical structures. This is certainly an ingenious hypothesis and might be accepted as an explanation were it not that, in some instances, the symptoms of the malady seem to be immediately induced by a few days of hard drinking and do not always occur during periods of sobriety, and, although the researches of Wagner (47) and Elzholz (48) have been directed towards the discovery of the anti-body, they have not as yet been successful.

The general opinion then seems to be that, while the mental symptoms of Korsakow's disease cannot be accounted for by the immediate action of alcohol upon the cortex, they do express the effects upon it of toxins of some kind. The general distribution of the lesions suggests that these toxins are conveyed in the blood stream, but, how they ultimately produce the changes in the nerve cells is still a matter of uncertainty. In the opinion of many German writers, the primary change occurs in the nerve fibres, the terminations of the cell processes; the morbid appearances seen in the cells are secondary and are of the same nature as those which occur in nerve cells when their processes have been severed experimentally, as by the section of a nerve. Ballet and his pupils, on the contrary, believe that it is the nerve cells which are first affected, and have described cases in which changes in the cells existed in the absence of any degeneration of the fibres; they consider that atrophy of the tangential and supra-radial fibres takes place at an early stage, because these fibres represent the portions of the neurons furthest removed from the nucleus, the source of nutrition.

I have already alluded to the view expressed by Dr. Mott that the changes within the nerve cells have a physical origin and are due to transudation of lymph causing an increase of their fluid contents ; there is, in other words, an œdema of the nerve cells. If œdema be responsible for the morbid change, then we may imagine that toxins in the blood give rise to it by so altering the constitution of the blood serum as to interfere with normal conditions of osmotic pressure, much in the same way as uræmic poisons are held responsible for the œdema of renal disease: the œdema would also be furthered by the feeble action of the heart and the low arterial tension, which so often exist in the disease.

Another cause of the œdema might be anæmia. I have already mentioned that similar changes in the nerve cells followed the anæmia experimentally produced in animals by temporary occlusion of the internal carotid arteries; the anæmic brains also which we find in cases of advanced and widespread disease of the cerebral arteries show œdema of the cortex and a great increase of the sub-arachnoid fluid. How far the changes in the cells of the cortex in Korsakow's disease may be the result of anæmia it is impossible to say. Korsakow (6) has observed the mental symptoms in a case of chronic palludism complicated by lymphadenoma, both of them conditions which give rise to anæmia, and my cases (Table I.) include five in which the symptoms followed severe hæmorrhages. On the contrary in the two cases (Cases 2 and 4, Group A) in which I made an examination of the blood, the number of red blood corpuscles was not diminished although the mental symptoms were well marked, and I am convinced, from the appearance of a large number of the cases, that if anæmia is present it is only very slight. In Cole's case (31) also, in which the disease was uncomplicated by any other condition during life, the histological examination, which was very carefully conducted, revealed little or no change in the walls of the arteries. I am therefore of opinion that though anæmia may sometimes assist in producing the changes in the nerve cells found in Korsakow's disease, it cannot be held entirely responsible for them.

VII.—DIAGNOSIS.

The nature of its symptoms suggests that a difficulty of diagnosis may arise between Korsakow's disease and other forms of mental affection in which there is both a diminished state of consciousness and a disturbance of the memory. Such conditions are epilepsy, hysteria, and according to some neurasthenia and general paralysis in some of its stages. The frequency, also, with which Korsakow's disease occurs in association with alcoholism renders it necessary to distinguish between it and other alcoholic mental affections. Finally, similar mental symptoms are encountered in cases of myxœdema, and, according to Wehrung (2), in forms of senile and arterio-sclerotic insanity.

Of all conditions with which Korsakow's disease may be confounded, the most important is general paralysis. I have already alluded more than once in this essay to the many points of similarity between the two affections, and the differential diagnosis between them has been specially treated by Séglas (11), Soukhanhoff and Bontenko (49), and Deroubaix (50). The features upon which this differential diagnosis is based vary according as a phase of Korsakow's disease is considered in which consciousness is much diminished or in which, consciousness being more fully preserved, the disturbance of memory is the prominent symptom. In the former case the clinical picture of the disease is not unlike that of general paralysis in its final stage. We see before us prostrate and bedridden patients, whose tissues may be so ill-nourished as to have given rise to the formation of bed-sores in situations of constant pressure. Mentally they are impervious to all external impressions; if sufficiently roused, they may utter a few incoherent remarks, but thereafter lapse immediately into unconsciousness. On examination symptoms pointing to affection of one or other of the cranial nerves may be detected. Such a condition well merits the term "pseudo-general paralysis" which has been applied to it. It is often difficult to make a definite diagnosis unless the course of

the case can be watched, but when this is possible, it may be observed that in Korsakow's disease the mind is at times perfectly clear; the patients reply rationally or make rational demands, or in some way show that the intellectual faculties are suspended rather than abolished. Definite signs of multiple neuritis or the presence of any such physical signs of alcoholism as dilated venules on the cheeks and nose or enlargement of the liver, would favour a diagnosis of Korsakow's disease. I have already alluded to the assistance which may be afforded by the condition of the heart.

The diagnosis is equally difficult when the symptoms of Korsakow's disease are confined to loss of memory and mental confusion. The various points upon which it depends in such cases have been well brought out by Séglas (11) in his lectures on mental disease delivered at the Salpêtrière. The facial expression of the subject of primitive mental confusion (with which affection this writer considers Korsakow's disease identical) differs from that of the general paralytic; the former, realising fully his shortcomings, is surprised by the sudden intrusion of realities into the train of his imagination and annoyed at his inability to reconcile the two; his face, therefore, expresses astonishment and alarm. The latter on the contrary, being unable to criticise his mental state, is satisfied with it, and his expression is one of contentment.

In both Korsakow's disease and general paralysis the mood of the patients may be apathetic, but an irritable mood, for the reasons just stated, is more usual in the former, as is also nocturnal excitability. The mood also changes frequently in both affections; but whereas, in Korsakow's disease, the change can be traced to some sufficient cause, in general paralysis it cannot be reasonably accounted for. In both affections there is false reminiscence, but the content of it in general paralysis, in distinction to Korsakow's disease, is not only improbable and absurd, but betrays a poverty of ideas, and the same may be said of the content of the delusions and hallucinations. Disorientation is also a symptom of general paralysis,

but it is never so complete as in Korsakow's disease; the paralytic may be, to some extent, unaware of his surroundings, but he can usually find his way about a familiar room, and though he may appear not to recognise persons, his actions show that he rarely mistakes the identity of those with whom he is habitually brought in contact. The way in which movements are executed in the two affections is a valuable aid to diagnosis. In Korsakow's disease the movements are slow and hesitating, and betray the consciousness of uncertainty; nevertheless, they are accurately performed, and eventually achieve their object. In general paralysis, on the contrary, they are performed deliberately and without hesitation, but are faulty and ataxic and often fail in their purpose.

I have already alluded to the distinctions which exist between the dysmnnesia of Korsakow's disease and the amnesia which is a symptom of an organic disease of the brain such as general paralysis; the nature and course of the latter show well that it is dependent upon no mere temporary loss of function, but upon irreparable statical change. Cases of Korsakow's disease, in which dementia has already shown itself, resemble general paralysis still more closely, nor is the problem of making a diagnosis mitigated by the observation of Baillarger that the mental symptoms of Korsakow's disease may complicate general paralysis itself at some time during its course, and for a time conceal its true nature. A good instance of this is afforded by the second case, which Séglas (11) demonstrated in his lectures.

For the sake of clearness, I shall give here in tabular form the various points of differential diagnosis which have just been considered.

	KORSAKOW'S DISEASE.	GENERAL PARALYSIS.
Facial expression ..	Of alarm and astonishment	Foolish, contented
Mood	More irritable, change traceable to some definite cause	Unaccounted for by circumstances
Pseudo-reminiscence..	Of a probable nature; usually related to some circumstances of the patient's past life and profession	Of an absurd and improbable nature; betrays poverty of ideation

		KORSAKOW'S DISEASE.	GENERAL PARALYSIS.
Disorientation..	..	Complete; patient has no idea of time or place or of the identity of persons	Incomplete; patient recognises familiar surroundings and persons with whom he is habitually brought in contact
Amnesia		Transient; more complete for the period of time concerned. Does not always obey the law of Ribot	Progressive, the material of the memory lost gradually, fact by fact, in order of its acquisition
Movements		Performed slowly and with hesitation, but so as ultimately to achieve their object	Performed deliberately, but are ataxic and do not achieve their object
Neuritis and other physical stigmata of alcoholism		Often present	Usually absent
Ocular and other cranial nerve symptoms		Transient and variable. Argyll Robertson phenomenon rare	Permanent. Argyll Robertson phenomenon common

The relations existing between Korsakow's disease and certain functional diseases of the nervous system.—I now propose to discuss certain affinities between Korsakow's disease, on the one hand, and such functional disorders as epilepsy, hysteria and neurasthenia, on the other. These latter affections have been termed "psychoneuroses," and however much we may be disposed to quarrel with the term, we must admit that the inclusion of physical symptoms distinguishes these affections from the different forms of functional insanity. Professor Janet (51) (52) has attempted a psychological explanation of the phenomena of hysteria and neurasthenia, and has shown, as I have pointed out elsewhere (53), that these two affections are merely different degrees of failure in the power of mental synthesis, of the power to assimilate in consciousness recent impressions with past experience. In hysteria this failure is sufficient to interfere greatly with perception; the field of consciousness is diminished. In neurasthenia, on the other hand, while all impressions may be said to reach consciousness, they are only very feebly assimilated, and lack that quality which is needed to produce in the mind of the individual a conviction of reality. According to Janet (52), a power of synthesis, too feeble to admit of

a high degree of conscious perception, can initiate lower forms of mental activity; these, which he calls "substitutions," constitute the accidents of hysteria and neurasthenia. In hysteria the substitutions take place entirely outside the sphere of consciousness; they are therefore not subjected to the criticism of the individual, and, through lack of inhibition, are more complete. They find objective expression in attacks of hysteria major, fixed ideas, neuro-mimesis, and divers forms of automatic conduct. In neurasthenia, the substitutions are not made entirely outside the sphere of consciousness; they are therefore subjected to a certain amount of criticism on the part of the individual, and are under his control. They find expression in the vague emotions, abstract rumination, ties and obsessive ideas with which we are familiar.

It requires but little stretch of the imagination to extend Janet's explanation to the phenomena of epilepsy, and Janet himself (52) has hinted that, in his opinion, these may be so explained. He assumes that in epilepsy the failure of mental synthesis is so complete that all conscious mental operations are completely abolished, and that the substituted forms of mental activity are, therefore, less inhibited and more complete even than in hysteria. The clinical facts of many cases show that often no strict line can be drawn between hysteria and epilepsy. It is true that in the various text-books of medicine certain criteria are offered by which an hysterical attack may be distinguished from an epileptic fit, but these are one and all based upon the recognition of the degree in which consciousness is present. If unconsciousness be so profound that the patient is unable to save himself from falling, or bites his tongue, or passes urine beneath him, then we call his condition epilepsy; if, on the other hand, consciousness is so far present as to admit of an effort on the part of the patient to save himself from falling, or to give him control over the function of micturition, we say that the attack was hysterical: the distinction is one of degree only and not necessarily of kind. This is more especially the case when we have to deal with atypical manifestations of epilepsy, the so-called substitu-

tions for the attack of *grand mal*, and it is difficult to say where the boundary is to be placed which separates the somnambulism of the hysterical individual from the automatic wandering of the epileptic. The term "hystero-neurasthenia" itself sufficiently indicates the difficulty which has arisen in some cases, in making a diagnosis between hysteria and neurasthenia, and Janet (52), although he draws many distinctions between these two conditions, admits the existence of transitional forms. There would appear then to be some ground for the assumption that the three affections, hysteria, neurasthenia, and epilepsy are but expressions of varying degrees of failure in the power of mental synthesis. If this be so, they can no longer be regarded as morbid entities, but will occur as symptoms of any condition in which this power is wanting. Alcoholism is such a condition, and we know that the three affections are often found in relation with it. My 245 cases of alcoholism include 21 cases of alcoholic epilepsy and 14 in which there were definite symptoms of hysteria, and symptoms of neurasthenia were present in a larger number than either. According to Bratz (54) alcoholic epilepsy is clinically indistinguishable from that we call idiopathic, and the only means he had of deciding in his own cases whether the epilepsy was primary or secondary to the alcoholism, apart from evidence afforded by the history, was that in the former the symptoms did not subside when all source of alcohol had been removed.

But we have seen that chronic alcoholism is the chief cause of another affection, also primarily dependent, as I have attempted to show, upon a failure of mental synthesis, an affection in which consciousness is always to some extent diminished. This affection is Korsakow's disease, and the question naturally arises, is there any relation between this malady and neurasthenia, hysteria and epilepsy, as they constitute symptoms of alcoholism? As regards epilepsy, cases 1, 2, 3, 7, Group B, show that the symptoms of Korsakow's disease may be ushered in by an epileptic fit, and Case 1, Group A, and some of Jolly's cases (*cf.* Table I.) are instances in which epileptiform attacks occurred at some

time or other during the course of the disease. Do these attacks of epilepsy differ in any essential from those which occur in alcoholism in which there are no symptoms of Korsakow's disease? We shall gain no information on this point from an appeal to morbid anatomy. Epilepsy, as I have urged, must be regarded merely as a symptom, and the morbid anatomical changes to which it has been ascribed are so various and conflicting that they can be only accidental: not a few of them may have been the basis of the dementia of which the epilepsy was a phase, and, indeed, few epileptics ultimately escape some degree of dementia; others, such as the minute hæmorrhages and areas of thrombosis described by John Turner (53), may have been agonal appearances or the result of prolonged status epilepticus. As a proof of the divers lesions which may give rise to symptoms of epilepsy, I am able to cite a case which came within my own experience, in which I found, after death, the typical lesions, both macroscopic and microscopic, of general paralysis, although the patient had been for many years regarded as an epileptic and placed in an epileptic ward of the asylum. Turner (55), however, demonstrated the presence of cells in the cortex of epileptics, showing appearances such as I have already described above, and such as were found by Cole in an uncomplicated case of Korsakow's disease. Cases of alcoholic epilepsy are also encountered in which the fit is followed by a short period of mental confusion and disorientation, and I am therefore of opinion that there is no distinction, save perhaps one of chronicity, between alcoholic epilepsy and the mental syndrome of Korsakow as it occurs in alcoholism.

A comparison between the mental state of Case 2, Group A, and that of Case 1, Group B, a case of alcoholism with hysterical symptoms, will show how many are the affinities between Korsakow's malady and hysteria. In both there is the same kind of disturbance of memory, the essential fault, as Raymond (28) has insisted, being a failure of evocation, or of the power to bring again before consciousness what has been assimilated in the past, a failure which varies much in intensity from day to day. According to

Raecke, an increase of irritability at night is common in hysteria, and he thus speaks of hysterical hallucinations, "Sie nehmen dieselben mehr die Form zusammenhängender Erlebnisse, als Analog den Ereignissen eines Traumes." Hysterical individuals are also the subjects of pseudo-reminiscence, and for this reason, like alcoholics, are often accused of wilful falsehood. Sollier (57) has observed mental confusion in hysteria at the time when the patients are passing from the state of somnambulism into one of full consciousness, and regards hysteria as a pathological form of sleep; after what has already been said, the similarity between this aspect of hysteria and the mental state in Korsakow's disease requires no further emphasis. In both affections also we witness automatic conduct, stereotyped poses, rigid and cataleptic, and other instances of katatonia.

What, then, is the distinction between the mental state in Korsakow's disease and hysteria? Chotzen, though he acknowledged the almost identical nature of the memory disturbance in both, remarked that in hysteria the onset and disappearance of the loss of memory was more sudden and its range more complete. In Korsakow's disease also, as opposed to hysteria, impressions received from the cutaneous surface and the retina seem to be consciously appreciated, for I have found the cutaneous sensibility and the range of the visual fields normal in all my cases in which the mental state of the patients rendered an examination possible. Here, again, the difference between the two affections would seem to be one of degree only.

I have pointed out above that the prodroma of Korsakow's disease may closely resemble the symptoms of primary neurasthenia; in both there is the same feeling of uselessness, the same indecision of purpose, the same irritable and unstable mood; only the course of the case may tell us from which of the two conditions the patient is suffering. Little distinction then would seem to exist, save one of degree, between the mental symptoms of Korsakow's disease and those of hysteria and neurasthenia as symptoms of alcoholism. I venture to suggest that the physical symptoms of

these affections may stand in an equally intimate relationship with the multiple neuritis. In many cases of multiple neuritis, before the disease shows itself definitely, the patients experience a general feeling of weakness and lassitude and suffer from vague shifting pains in various parts of the body, symptoms not easily to be distinguished from those of neurasthenia, and Raymond (28) has pointed out that certain features of neuritis in the period of full development, the sudden onset of paraplegia, the astasia abasia, the distribution of the cutaneous anæsthesia and the peculiar tetanic character of the knee jerk, indicate rather a disturbance of function than organic changes in the nerves themselves (*cf.* Case 2, Group D).

The histological changes in the neurons which presumably underlie the symptoms of Korsakow's disease, have been described, and the general nature of their distribution insisted on. Is it too much to assume that in cases of alcoholism in which, although the symptoms of Korsakow's disease never show themselves definitely, those of either neurasthenia or hysteria or even epilepsy occur, the change in the nerve cells has already begun but has not yet reached a stage at which it could be demonstrated by the microscope?

The diagnosis between Korsakow's disease and some other affections.—In Wehrung's paper allusion is made to the close similarity between Korsakow's disease and senile dementia, and the various points of differential diagnosis are stated categorically. In the latter affection besides the mental confusion and the peculiar disturbance of memory, there is, according to this writer, a progressive failure of the intellectual faculties, an early loss of the power of logical argument, an impoverishment of the imagination, a loss of the ethical sense, a lapse from altruism into egotism, and a more positive tendency towards depression or exaltation.

A sluggishness of mind with no true disturbance of ideation, a failure of the memory and a mood alternating between apathy and irritability, are symptoms sometimes encountered in cases of myxœdema, and, when the physical

condition peculiar to this disease is not pronounced, may give rise to difficulty in diagnosis. I saw at the Claybury Asylum a myxœdematous imbecile, who, from the nature of her symptoms, had been diagnosed as a case of alcoholism with Korsakow's disease, although there was no proof of the existence of the alcoholic habit; there had been no symptoms of neuritis save some pain and tenderness of the legs.

The mental symptoms of Korsakow's disease occurred, according to Mönkemöller and Kaplan (17), in a case of cerebral tumour, and were attributed by these writers to the action of toxins absorbed from the tumour itself upon the cells of the cortex. In 57 of the 775 cases of cerebral tumour with mental symptoms collected by Schuster (58), there were mental confusion and delirium with hallucinations, and in three the mental state of the patients was akin to that of Korsakow's disease. In those cases of cerebral tumour with mental symptoms which have come within my own experience, these symptoms differed in some respects from those of Korsakow's disease; the mood of the patients, it is true, was apathetic, often euphoric, but the ideation was retarded rather than confused, and the reaction time was therefore lengthened. The loss of memory in cases of tumour also is progressive, and more like that which is a symptom of organic disease.

Pearson (59) has called attention to the atypical nature of the symptoms of tuberculous meningitis when it occurs in adults. The possibility of this affection must never be neglected in cases of alcoholism, of which it is indeed not infrequently a terminal event, and cases 5 and 6, Group E, show how easily the presence of tuberculous meningitis in a case of chronic alcoholism may escape notice during life.

Before concluding my remarks on diagnosis, I must briefly allude to the distinctions between Korsakow's disease and the more acute forms of alcoholic insanity. These affections have been recently studied by Bonhöffer (8), Kraepelin (10), Meyer (15) and Luther (16). Luther mentions (i.) a form of alcoholic paranoia; (ii.) a form of acute hallucinatory insanity with or without delirium; (iii.) a

form of insanity of which exaltation and delusions of grandeur are the chief symptoms. All these forms of insanity, unlike Korsakow's disease, occur early in the course of alcoholism among persons with an insane inheritance. There is in them little interference with the state of consciousness; the delusions and hallucinations, therefore, lack the dream-like nature of those which occur in Korsakow's disease, and are more liable to become systematised in these affections; also hallucinations of hearing are more common than hallucinations of vision.

VIII.—COURSE AND TERMINATION.

In 33 per cent. of the cases (Table I.) the mental symptoms disappeared within a year of their inception; in 14 per cent. they lasted for more than a year, and in 6 per cent. for more than three years. In most cases, however, some slight failure of the memory persists indefinitely.

Termination by complete recovery is noted in 15 per cent. of the cases, some amelioration of the symptoms in 30 per cent., and death occurred in 28 per cent. Pulmonary tuberculosis was the cause of death in five instances, exhaustion and cardiac failure in seven, pneumonia in four, an epileptic attack in two, cancer of the stomach in one, and granular kidney in one.

IX.—PROGNOSIS.

I need add little to what I have already written on the subject of prognosis. That as to life will largely depend upon the general physical condition of the patients, and yet, curiously enough, even when this amounts to the cachexia which we find at the end of some wasting disease, complete recovery ultimately may take place (Cases 2, 4, 5, Group A). Under suitable treatment, much improvement of the mental symptoms may be looked for, but in alcoholic cases a relapse is always to be feared, because of the almost universal tendency of the patients to fall again into habits of intemperance. A complete restoration of the mental

faculties is, I am convinced, very rare, much more so than would appear from my figures (Table I.): indeed, from the very nature of the morbid anatomy of the disease, some permanent dementia must remain in all but the very mildest cases, clinical evidence of which is usually afforded by some degree of progressive failure of the memory, and a permanent alteration of the mood. In alcoholic cases, if the habit be resumed, the mental state of the patients will end in complete dementia, towards which Korsakow's disease, both clinically and anatomically, must be regarded as the first step. Even were the patient to abandon his habit, when alcoholism has reached the advanced stage at which symptoms of Korsakow's disease usually appear, the liver and kidneys and the gastro-intestinal tract are so irreparably damaged, and their functions so deranged, that the nerve cells are continually in danger of being exposed to the influence of an auto-intoxication, and it requires then but some slight accident to determine an attack of the malady.

X.—TREATMENT.

The treatment in Korsakow's disease should be rational, and based upon indications afforded by the condition of the patients, and upon our conception of the etiology and pathogenesis. It is important to bear in mind the wide distribution of the morbid process. The disease is not only a mental one but may affect the nervous system in general, any part of which must be regarded as in jeopardy, even when the mind alone appears to be affected. The state of the patients is, at the least, one of profound exhaustion, and this applies not only to the nervous system, but to the heart, and, indeed, to the body in general. The truth of this assertion is obvious when the multiple neuritis is severe and the prostration extreme, but unfortunately it often fails to be recognised in those cases in which physically the patients appear to be in good health. For this reason, I hold it advisable to prescribe absolute rest in bed in all cases, for weeks, and even months, according to their severity. To ensure complete

rest for the mind, strict isolation should be practised, and every source of worry or fatigue be removed.

Attention must next be directed towards removing the patient from the influence of the morbid agent which has given rise to his symptoms. Except in cases of emergency, the use of alcohol in any form should be forbidden; even where the malady can be traced to some other definite cause, alcohol can but aggravate the mischief, and besides, as I have stated above, there are but few cases for which alcoholism will not be found in part responsible, if the antecedents of the patient be inquired into with sufficient care.

The possibility that the symptoms may be due to an auto-intoxication arising from hepatic or gastro-intestinal inadequacy is a sufficient reason for putting the patient upon a bland diet. The best form of food is milk, to which eggs and farcinaceous substances may be added; fish is unobjectionable, but butcher's meat, strong soups and the various forms of meat essence should be proscribed because of the extractives they contain. In alcoholic cases, in which there is often much gastritis, it may be well to wash out the stomach as a preliminary measure, and afterwards to administer food in small quantities at a time, and to adopt measures to relieve vomiting and to promote the appetite. The excretory functions should be assisted in order to rid the body, as far as possible, of the *materies morbi*. For this purpose habitual saline purgation is very valuable; an initial dose of calomel or blue pill may be of advantage, but systematic dosage with mercury should not, I think, be resorted to because of the effects of this drug upon the peripheral nerves. The restoration of the nervous elements will best be effected by rest and food. Arsenic is, for obvious reasons, inadvisable, but strychnine is a valuable drug for the neuritis, especially when given in the form of hypodermic injections. The condition of the heart calls for special treatment, and where rest and food do not succeed in affecting improvement, the use of digitalis may be necessary. This drug is also valuable because of its tonic effect on the walls of the arteries, and because it aids

excretion by increasing the output of urine. In those cases in which there is any reason to suspect that anæmia may have assisted in producing the symptoms, iron in some form should be given.

Of special symptoms the sleeplessness is often difficult to combat; morphia, especially in the form of injections, should be avoided, for the morale of most of these patients is such that they may easily develop the morphia habit; moreover, the drug destroys the appetite, retards the processes of digestion, and, by causing constipation, interferes with excretion. Chloral is sometimes contra-indicated by the condition of the heart. An hypnotic may have to be found to suit the individual case; of other drugs of the kind, I have often found bromidia, chloralamide or paraldehyde effectual, but the action of veronal uncertain. When there is much delirium at night, however, the ordinary use of hypnotics may fail, and rectal injections of chloral and bromides must be resorted to.

When convalescence is well established, the patients may try rest, with moderate exercise and a change of habitation, but they should still avoid all irregular sources of mental fatigue; some form of psychotherapy, however, may be adopted with advantage, such as forcing the patients to concentrate the mind upon some definite intellectual pursuit for a short time each day. Every effort must be made to dissuade the patients from the idea that they are mere mental wreckage; confidence should be placed in them with regard to their habit, and their sense of ethical responsibility, in particular, should be encouraged. In the case of alcoholics, such an after-treatment may be carried out with advantage in some reliable institution where they can be kept under supervision.

No form of treatment by suggestion either in the hypnotic or waking state, in my opinion, is justifiable in these cases; the mental operations of the patients are only too apt to be performed automatically, and every effort should be used to rouse them from their dream state and to assist their powers of concentration.

Lastly, I would urge that patients suffering from

Korsakow's disease be not treated in asylums, even though their mental condition may seem to warrant a certificate of insanity. Apart from the fact that the present organisation of these institutions in England, with but few exceptions, hardly admits of a strict isolation treatment, with special diet and trained nursing, the subjects of Korsakow's disease are not truly insane, but delirious, and as soon as consciousness is fully restored, which happens very speedily under suitable treatment, they act and think rationally enough. It is then both depressing and demoralising for them to find themselves in the company of the demented and of those suffering from other forms of incurable insanity. Suicide need hardly be apprehended; the impulse to it, if present, like the other mental symptoms, is transient, and though the patients sometimes threaten self-destruction, they rarely make any determined attempt to accomplish it.

The existence of mental affections, such as Korsakow's disease, is one of the strongest arguments in favour of the establishment of a psychiatric hospital in London, such as already exists in Munich, and whose institution in America has been so ably advocated by Paton (60).

XI.—CONCLUDING REMARKS.

In the foregoing account of Korsakow's disease I have endeavoured to show that there may be associated with alcoholism a certain affection of the mind, whose chief symptoms are a failure of attention and of the power of immediate recollection. The former occasions a diminished state of consciousness, varying in its expression from a few isolated symptoms of mental confusion to a condition of profound stupor. The removal of consciousness gives free play to a train of delirious ideas, which constitute a kind of dream representing some scene in the past life of the patients, usually concerned with their profession or occupation. Certain symptoms of secondary importance, delusions and hallucinations, are a part of this dream rather than of the full state of consciousness.

As a possible basis for these symptoms there are certain definite changes of the cells and tracts of the cerebral cortex; the latter are probably of a permanent nature, but the former are often such as to permit of a complete restoration to the normal. The changes are not limited to the cerebral cortex, but may affect other parts of the nervous system, and when they do so they give rise to a multiple neuritis, in which certain of the cranial nerves may be included.

The mental symptoms, as the morbid anatomy of the disease suggests, may disappear almost entirely, and are in no sense an evidence of alcoholic dementia, for which, however, they are commonly mistaken. Nevertheless, they must be regarded as a first step towards dementia, and with the neuritis they form clinically, and perhaps anatomically, a link, connecting the so-called functional diseases of the nervous system with those which depend upon a true degenerative change.

Korsakow's disease is not an affection peculiar to alcoholism; nevertheless, a typical instance of it rarely occurs in any other connection; it accompanies the latter rather than the earlier stages of alcoholism, and is more prone to occur in individuals with a sound mental inheritance than in those disposed to insanity.

The pathogenesis of the disease is still obscure. While it is fairly certain that the symptoms do not express a direct action of alcohol itself upon the structures of the nervous system, they are generally held to be the result of some form of toxæmia, possibly of an auto-intoxication. Whether the toxins in the blood give rise to the symptoms by producing an œdema of the nerve cells, as the morbid anatomical changes have seemed to suggest, we cannot at present say. Similar changes have followed anæmia of the brain, experimentally produced in animals by ligature of the internal carotid arteries, and though there is little evidence that anæmia itself is ever entirely responsible for the symptoms of Korsakow's disease, it may assist in giving rise to them in a few instances.

Korsakow's disease, as I have already remarked, must

not be confounded with alcoholic dementia; it has also to be distinguished from general paralysis, which it closely resembles in many particulars. Many of its features also, as I have attempted to show, are common to those of hysteria, epilepsy and neurasthenia, especially when these affections are symptoms of alcoholism.

In conclusion, I would point out that the study of Korsakow's disease helps us to distinguish between two important classes of mental affection: those in which the morbid ideas take place in a complete state of consciousness, and those in which they occur when consciousness is suspended and constitute delirium. As an instance of the former, I may mention paranoia. In paranoia consciousness is always fully retained; the morbid ideas occur, as it were, when the individual is fully awakened; they are, therefore, convincing to him and may cling to him indefinitely. On the other hand, epilepsy, hysteria, dementia præcox, general paralysis in some of its phases, and Korsakow's disease, are instances of the latter. In these affections the consciousness of the individual is rarely complete, and his morbid ideas are, so to speak, part of a dream; they therefore vanish and leave no permanent impression behind.

In alcoholism we may encounter illustrations of either class of mental affection, but it was perhaps in reference to Korsakow's disease that Lasègue wrote, "*La delire alcoolique n'est pas une delire, c'est une rêve.*"

REFERENCES.

- (1) TILING. "Ueber die bei der Alkoholischen Neuritis beobachtete Geistesstörung," *Allgemeine Zeitschrift für Psychiatrie*, 1890, S. 223-257.
- (2) WEHRUNG. "Beitrag zur Lehre von der Korsakowschen Psychose," *Archiv für Psychiatrie und Nerven Krankheiten*, 1905, Band xxxix., Heft 2.
- (3) FISCHER. "Ueber eine Eigenthümliche Spinal Erkrankung bei Trinkern," *Archiv für Psychiatrie und Nerven Krankheiten*, 1882, Band ii.
- (4) STRUMPELL. "Zur Kenntniss der Multiplen Degenerativen Neuritis," *Archiv für Psychiatrie und Nerven Krankheiten*, 1883, S. 339.
- (5) LILIENFELD. "Zur Lehre der Multiplen Neuritis," *Berliner Klinische Wochenschrift*, 1885, p. 727.
- (6) KORSAKOW. "Ueber eine besondere Form psychischer Störung combinirt mit Multipler Neuritis," *Archiv für Psychiatrie und Nerven Krankheiten*, 1890, Band xxii., S. 609-704.
- (7) KORSAKOW. "Eine psychische Störung combinirt mit Multipler Neuritis," *Allgemeine Zeitschrift für Psychiatrie*, 1890, Band xlv.
- (8) BONHÖFFER. "Die akuten Geisteskrankheiten der Gewohnheitstrinker."
- (9) E. MEYER & RAECKE. "Zur Lehre von Korsakowschen Symptomen complex," *Archiv für Psychiatrie und Nerven Krankheiten*, 1903, No. 1, Band xxxviii.
- (10) KRAEPELIN. Article on "Chronic Alcoholism," "Lehrbuch der Psychiatrie."
- (11) SÉGLAS. "Léçons cliniques sur les maladies mentales," p. 149, Paris, 1895.
- (12) CHASLIN. "La confusion mentale primitive," Paris, 1895.
- (13) JOLLY. "Ueber die psychischen Störungen bei Polyneuritis," *Charité Annalen*, 1897, Band xxii., S. 579, *et seq.*
- (14) HILL, BUCHAN. "Some Aspects of Alcoholism," *Review of Neurology and Psychology*, 1905, vol. iii., Nos. 1, 2, 3, 5.
- (15) E. MEYER. "Bei der Entstehung ueber acute und chronische Alkoholpsychosen und ueber die ætiologische Bedeutung des chronischen Alcohol-misbrauchs," *Archiv für Psychiatrie*, 1905, Band xxxviii., Heft 1.
- (16) LUTHER. "Zur Casuistik der Geistesstörung auf dem Boden des chronischen Alcoholisms," *Allgemeine Zeitschrift für Psychiatrie*, 1902, Band lix., p. 20.
- (17) MÖNKEMÖLLER & KAPLAN. "Symptomatischer Korsakow und Rückenmarks Erkrankungen bei Hirn tumor," *Allgemeine Zeitschrift für Psychiatrie*, 1899, Band lvi., p. 701.
- (18) DUPRÉ. Article on "Psycho-polyneuritis," "Traité de Pathologie Mentale," by GILBERT BALLET and others, p. 1122.
- (19) MÖNKEMÖLLER. "Casuistischer Beitrag zur sogenannten Polyneuritische Psychose (Korsakowsche Krankheit)," *Allgemeine Zeitschrift für Psychiatrie*, 1897, Band liv., p. 806.

- (20) BÖDEKER. "Ueber einen acuten und einen chronischen Fall von Korsakowsche Psychose," *Archiv für Psychiatrie und Nerven Krankheiten*, Band xl., Heft. 1, S. 304.
- (21) KALBERAH. "Ueber die acute Commotions-psychose zugleich ein Beitrag zur Ätiologie des Korsakowschen Symptomen-complex," *Archiv für Psychiatrie und Nerven Krankheiten*, 1904, Band xxxviii., Heft 2, S. 402.
- (22) NINA RODRIGUES. "La psychose polynévritique et le Béri-Béri," *Annales Medico-psychologiques*, Mars, Avril, 1906.
- (23) RAYMOND. "Clinique des maladies du Système Nerveux," Paris, 1897, Deuxième Series, Cap. i., 74.
- (24) BEVAN LEWIS. Article on Alcoholic Insanity, "Text-book of Mental Diseases."
- (25) DE FLEURY. "Les symptômes et la traitement de Neurasthénie." Paris, 1902.
- (26) SMITH. "The range of Immediate Association and Memory in Normal and Pathological Individuals," *Archives of Neurology*, vol. ii., p. 767.
- (27) CHOTZEN. "Zur Kenntniss der polyneuritischen Psychose," *Allgemeine Zeitschrift für Psychiatrie*, Band lix., Heft 4, 1902, Articles 1 and 2.
- (28) RAYMOND. "Clinique des maladies du Système Nerveux." Paris, 1897, Deuxième Series, Cap. viii.
- (29) KORSAKOW. "Ueber Erinnerung-täuschungen (Pseudo-reminiscenzen) bei polyneuritischen Psychose," *Allgemeine Zeitschrift für Psychiatrie*, Band xlviii., 1891.
- (30) KRAEPELIN. "Ueber Erinnerungsfälschungen," *Archiv für Psychiatrie und Nerven Krankheiten*, 1896, Band xvii., S. 830.
- (31) S. COLE. "Systematic Examination of the Central and Peripheral Nervous System and Muscles in a Case of Acute Alcoholic Paralysis with Mental Symptoms," *Archives of Neurology*, vol. ii., p. 836.
- (32) JOHN TURNER. "Accounts of Twelve Cases of Psycho-polyneuritis in Women," *Journal of Mental Science*, 1903.
- (33) KAHLBAUM. "Klinische Beobachtung zweier Fälle von polyneuritischer Psychose (dysphrenia alcoholica polyneuritica)," *Allgemeine Zeitschrift für Psychiatrie*, 1899, Band lvi.
- (34) ALLCHIN. "System of Medicine," article on Alcoholism.
- (35) FREUND. "Klinische Beiträge zur Kenntniss der Generellen Gedächtniss-schwache," *Archiv für Psychiatrie und Nerven Krankheiten*, 1889.
- (36) S. COLE. "On the Changes in the Central Nervous System in the Neuritic Disorders of Chronic Alcoholism," *Brain*, Autumn, 1902.
- (37) BALLET FAURE. "Contribution à l'anatomie pathologique de la psychose polynévritique et de certaines formes de confusion mentale primitive," *Presse Médicale*, 1898, No. 98.
- (38) BABINSKI. "Les névrites," "Traité de Médecine" (Charcot & Bouchard), vol. vi., Paris, 1884.
- (39) CHANCELLAY. "Contribution à l'étude de la psychose polynévritique," "Thèse de Paris," 1901.
- (40) ALZHEIMER. "Histologische Studien zur Differenzial-diagnose der progressiven Paralyse," Jena, 1904.
- (41) GÜDDEN (quoted by Wehrung [2]), *Archiv für Psychiatrie und Nerven Krankheiten*, Band xxviii., 1896, S. 42, Fall. iii.

- (42) SIEFERT. "Zur Anatomie der Polyneuritischen Psychose" (quoted by Wehrung [2]), *Archiv für Psychiatrie*, 1901, and *Neurologisches Centralblatt*, 1900, S. 1, 134.
- (43) RAIMANN. "Polioencephalitis superior acuta und Delirium Alcoholicum als Einleitung einer Korsakowschen Psychose ohne polyneuritis," *Wiener Klinische Wochenschrift*, No. 2, 1900.
- (44) BALLEZ. "La psychose polynévritique," Dixième Congrès des Médecins Aliénistes et de Neurologistes à Marseilles (Abstract), *Revue de Neurologie*, 1899, No. 8.
- (45) LEOPOLD LEVI. "Troubles nerveux d'origine hépatique," "Thèse de Paris," 1896.
- (46) HERBER. "Chemical Physiology," pp. 319-320.
- (47) WAGNER. "Die Giftwirkung des Alkohols bei einigen nervösen und psychischen Erkrankungen" (quoted by Wehrung [2]), *Wiener Klinische Wochenschrift*, 1901, April 11.
- (48) ELZHOZ. "Ueber die Bezeichnungen der Korsakowschen Psychose zur polioencephalitis superior hæmorrhagica" (quoted by Wehrung [2]), *Wiener Klinische Wochenschrift*, 1900, S. 337.
- (49) SOUKHANOFF & BONTENKO. "Sure diagnostic différentiel de la maladie de Korsakoff," *Journal de Neurologie*, 20 Novembre, 5 Decembre, 1903.
- (50) DEROUBAIX. "Syndrome de Korsakoff et paralysie générale," *Journal de Neurologie*, 5 Decembre, 1903.
- (51) P. JANET. "Les symptômes et les accidents d'hystérie," 2 vols, Paris, 1896.
- (52) P. JANET. "Les obsessions et la psychasthénie," Paris, 1903.
- (53) ASCHERSON. "Some Distinctions between Hysteria and Neurasthenia," *Practitioner*, September, 1904.
- (54) BRATZ. "Alkohol und Epilepsie," *Allgemeine Zeitschrift für Psychiatrie*, Band lvi., 1899.
- (55) TURNER. "Pathological Anatomy of Idiopathic Epilepsy," Proceedings of the Neurological Society; *Brain*, 1905 Autumn and Winter No., p. 592.
- (56) RÄCKE. "Zur Lehre vom hysterischen Irrensein," *Archiv für Psychiatrie und Nerven Krankheiten*, Band xl., Heft 1, p. 173.
- (57) SOLLIER. "La nature et genèse d'hystérie," Paris, 1903.
- (58) SCHÜSTER. "Psychische Störungen bei Hirntumoren," 1902 (quoted by SOUKHANOFF and BONTENKO).
- (59) PEARSON. "Tuberculous Meningitis in Adults," Medical Publishing Co., December, 1902.
- (60) PATON. "Psychiatry," London: Lippincott, 1905, cap vi., p. 169 ?.

TABLE I.
ANALYSIS OF THE CLINICAL FEATURES OF 126 CASES OF KORSAKOW'S DISEASE.

Feature analysed	Korsakow	Jolly	Meyer and Raecke	Tilling	Kahlbaum	Mönkemöller and Kaplan	Chotzen	Bödeker	Mönkemöller	Turner	Author	Total	Per cent.
Cases :	6	21	8	7	2	1	5	2	24	12	38	126	—
ÆTIOLOGY.													
Age, average: Male	40	40	53	42	50	—	45	55	48	44	50	46	—
„ „ Female	47	44	43	43	49	49	48	—	57	44	40	46	—
„ „ Total	46	41	50	42	49	49	46	55	50	44	44	46	—
Sex: Male	1	14	6	6	1	0	3	2	19	0	19	71	59.5
„ Female	5	7	2	1	1	1	2	0	5	12	19	55	40.5
DISPOSING INFLUENCES.													
Family history of alcoholism	—	—	1	—	1	—	—	1	—	—	2	5	4
„ „ insanity ..	—	1	3	—	1	—	—	1	—	—	4	10	8
Family history of other nervous affections	1	1	1	—	—	—	—	2	—	—	6	11	8.8
Previous history of nervous instability	—	2	1	—	1	—	—	1	—	—	3	8	6.4
Previous history of fits ..	—	1	2	—	—	—	3	—	5	—	3	14	11.2
„ „ apoplexy	1	—	—	—	—	—	1	—	—	—	1	3	2.4
„ „ syphilis	1	—	3	2	—	—	—	1	—	1	3	11	8.8
Previous history of exposure to lead	—	1	—	—	—	—	—	—	—	—	2	3	2.4
Previous history of rheumatic fever	—	1	—	—	—	—	—	1	3	—	4	9	7.2
Previous history of malaria	2	—	—	—	—	—	—	—	—	—	1	3	2.4
ASSOCIATED DISEASE, OR CONDITION.													
Alcoholism	2	20	5	6	2	1	5	2	21	10	33	112	89
Pulmonary tuberculosis ..	1	4	—	—	—	—	2	—	—	—	6	13	10.8
Alcoholism + pulmonary tuberculosis	—	4	—	—	—	—	2	—	—	—	6	12	9.6
Typhoid fever	2	—	—	—	—	—	—	—	2	—	—	4	3.2
Influenza	—	1	—	—	—	—	—	—	3	—	2	6	4.8
Erysipelas	—	—	—	—	—	—	—	—	—	—	2	2	1.6
Arterio-sclerosis	—	—	—	—	—	—	—	1	2	—	3	6	4.8
Cardiac hypertrophy	—	—	1	—	—	—	—	1	2	—	2	6	4.8
Valvular disease of heart ..	1	—	—	—	—	—	—	—	1	—	2	4	3.2
Pulmonary disease other than tuberculosis	—	3	1	—	1	—	2	1	2	—	10	20	16
Excessive use of tobacco ..	—	—	—	—	—	—	—	1	4	—	2	7	5.6
Cerebral tumour	—	—	—	—	—	1	—	1	—	—	—	2	1.6
Hepatic disease	—	—	1	—	—	—	—	—	2	—	23	26	20.6
Renal disease	—	—	—	—	—	—	—	—	6	—	2	8	6.4
Gastro-intestinal disease ..	5	3	2	3	—	—	2	—	4	1	15	35	28
Disease of female generative organs	2	—	—	—	—	—	—	—	—	—	—	2	1.6
Cancer	—	—	—	—	—	—	—	—	1	—	—	1	0.8
Lymphadenoma	1	—	—	—	—	—	—	—	—	—	—	1	0.8
Arsenical medication	1	—	—	—	—	—	—	—	—	—	—	1	0.8
Forms of sepsis	1	—	—	2	—	—	—	—	—	—	1	4	3.2

TABLE I.—Continued.

Feature analysed	Korsakow	Jolly	Meyer and Raecke	Tiling	Kahlbaum	Mönkemöller and Kaplan	Chotzen	Bödeker	Mönkemöller	Turner	Author	Total	Per cent.
Cases :	6	21	8	7	2	1	5	2	24	12	38	126	—
SPECIAL DETERMINING CAUSE.													
Recent excessive indulgence in alcohol	—	—	2	1	—	—	—	—	1	1	2	7	5.6
Recent mental shock or worry	2	2	3	—	—	1	—	—	1	—	5	14	11.2
Severe hæmorrhage	1	—	1	—	—	—	—	—	—	—	3	5	4
Persistent severe vomiting ..	4	1	1	2	—	—	2	—	4	—	5	19	15.1
„ diarrhoea	—	1	—	—	—	—	1	—	1	—	5	8	6.4
Recent jaundice	—	—	—	—	—	—	—	—	—	—	1	1	0.8
Apoplectic seizure	1	—	1	—	—	—	—	—	—	—	—	2	1.6
Syncopal attack	—	—	—	—	—	—	—	—	—	—	1	1	0.8
Head injury	—	1	—	1	—	—	—	—	—	—	—	2	1.6
MODE OF ONSET.													
Gradual onset	3	3	4	5	—	1	4	—	7	1	6	34	27
Sudden onset	3	6	4	2	1	—	—	1	11	2	15	45	36
Onset with delirium tremens	—	3	3	1	1	—	1	—	6	3	2	20	16
Onset with convulsions or sudden loss of consciousness	—	3	2	—	—	—	—	—	4	—	6	15	12
MENTAL SYMPTOMS—PRODROMA.													
Irritability	—	—	2	—	—	—	3	—	2	—	—	9	7.2
Sleeplessness	—	—	2	—	—	—	2	—	1	—	—	5	4
Suspicion	—	—	—	—	—	—	—	—	1	—	—	1	0.8
Suicidal impulse	—	—	—	—	—	—	—	—	1	—	—	1	0.8
Failure of memory	1	2	2	1	—	1	3	—	5	—	1	16	12.8
Failure of attention	—	—	—	—	—	—	—	—	1	—	—	1	0.8
General uselessness—loss of initiative, energy, depres- sion, &c. (Psychasthenia) ..	2	1	3	1	—	—	2	—	3	2	2	16	12.8
MENTAL SYMPTOMS—GENERAL.													
Progressive failure of memory	—	2	2	1	—	—	2	1	3	2	2	15	12
Functional disturbance of memory	6	16	8	7	2	1	5	2	20	11	25	103	81.7
Pseudo-reminiscence, confab- ulation	6	12	8	5	2	1	4	2	21	9	18	88	70.4
Disorientation in time	5	18	8	4	2	1	5	2	19	10	17	91	72.1
„ „ place	4	15	8	4	2	1	5	2	21	10	19	91	72.1
Confusion of personal identity	5	6	5	3	2	1	4	2	17	4	9	58	45.6
Hallucinations of vision	1	2	3	—	2	1	2	2	3	2	5	23	18.2
Zoopsia	1	1	2	—	1	1	—	—	1	2	2	11	8.8
Hallucinations of hearing	—	—	—	—	2	1	—	—	—	1	1	5	4
Hallucinations of touch	—	—	—	—	—	—	—	—	—	—	1	1	0.8
Morbid suspicion, ideas of persecution	1	1	3	—	2	1	1	1	5	1	5	21	16.8
Morbid jealousy	—	—	—	—	—	—	1	—	—	—	2	3	2.4
Delusions of grandeur	—	—	2	—	1	—	—	—	—	1	1	5	4
Delusions of a sexual or marital nature	—	—	1	—	—	—	—	—	—	4	1	6	4.8
Delusions of a religious nature	—	—	1	—	—	—	—	—	—	—	—	1	0.8

TABLE I.—Continued.

Feature analysed	Korsakow	Jolly	Meyer and Raecke	Tilling	Kahlbaum	Mönkemöller and Kaplan	Chotzen	Bödeker	Mönkemöller	Turner	Author	Total	Per cent.
Cases :	6	21	8	7	2	1	5	2	24	12	38	126	—
MENTAL SYMPTOMS—Contd.													
Delusions of an hypochondriacal nature	—	—	—	—	—	—	—	—	1	—	—	1	0.8
Suicidal tendency	—	2	1	—	—	—	—	—	—	—	—	3	2.4
Homicidal tendency	—	—	—	—	—	—	1	—	—	—	—	1	0.8
ALTERATIONS OF MOOD.													
Euphoria and gaiety	—	2	3	1	2	1	1	2	9	9	11	41	32.6
Jocularity	—	—	3	—	—	1	—	1	5	1	4	15	12
Apathy	1	3	3	2	—	—	4	—	—	2	2	17	13.5
Depression	—	2	4	—	—	1	1	—	2	—	—	10	8
Irritability	—	4	1	—	1	—	2	—	1	1	7	17	13.5
Querulousness	—	—	—	—	—	—	3	—	5	—	2	10	8
Fear and anxiety	1	2	3	1	2	—	—	—	1	1	1	12	9.6
Excitability	2	2	6	2	2	—	—	—	4	6	8	32	25.6
Emotionalism	—	—	3	1	—	1	—	1	3	5	1	15	12
ALTERATIONS IN CONDUCT.													
Rudeness and impulsiveness	—	2	1	1	—	—	—	—	1	2	1	8	6.4
Failure in ethical sense	—	1	—	—	1	—	—	—	1	2	2	7	5.6
OTHER MENTAL SYMPTOMS.													
Sleeplessness	—	—	2	2	—	—	2	—	2	—	—	8	6.4
Motor unrest	1	1	5	—	2	—	3	1	1	2	3	19	15.1
Delirium	—	6	1	—	—	—	3	—	—	—	3	13	10.3
Somnolence	1	—	3	—	—	1	2	—	—	1	—	8	6.4
Stupor	1	—	3	—	—	1	1	—	3	—	2	11	8.8
Catatonia	—	—	1	—	—	—	—	1	—	—	2	4	3.2
Automatism — stereotyped movements	—	—	1	—	—	—	—	—	—	—	1	2	1.6
Wet and dirty habits	—	1	5	—	2	—	1	—	4	3	5	21	16.8
Nocturnal increase of excitability or restlessness	4	4	4	1	1	1	1	—	4	1	15	36	28.8
SYMPTOMS POINTING TO ASSOCIATED PSYCHONEUROSIS.													
Evidences of psychasthenia	1	—	2	—	—	—	1	—	2	—	1	7	5.6
„ hysteria	—	4	2	1	—	1	—	—	—	2	2	12	9.6
Symptoms of an epileptic nature	—	6	4	—	1	1	—	—	4	1	8	25	20.2
PHYSICAL SYMPTOMS OF THE NERVOUS SYSTEM.													
Well-marked multiple neuritis	5	13	—	7	—	—	2	—	8	10	16	61	48.4
Slight multiple neuritis	1	6	4	—	2	—	3	—	13	2	7	39	30.9
No evidence of multiple neuritis	—	2	4	—	—	1	—	1	3	—	15	26	20.6
Aphasia, motor	1	1	—	—	1	—	—	—	1	—	1	5	4
„ sensory	—	1	—	1	1	—	1	—	—	—	—	4	3.2
Speech : Articulatory disturbance	3	2	3	2	1	—	4	—	2	1	4	22	17.6

TABLE I.—Continued.

Feature analysed	Korsakow	Jolly	Meyer and Raecke	Tilling	Kahlbaum	Mönkemöller and Kaplan	Chotzen	Bodeker	Mönkemöller	Turner	Author	Total	Per cent.
Cases :	6	21	8	7	2	1	5	2	24	12	38	126	—
PHYSICAL SYMPTOMS—Contd.													
Disturbance of handwriting	—	—	—	—	—	—	1	—	—	—	—	1	0.8
Tremor of tongue ..	2	3	5	—	1	—	5	—	2	1	6	25	20
„ facial muscles ..	—	—	—	—	—	—	—	—	1	—	2	3	2.4
„ hands ..	—	3	3	2	1	1	4	—	4	1	3	22	17.6
Eye: Inequality of pupils ..	—	2	2	—	—	1	—	—	2	3	3	13	10.3
„ Pupils sluggish to light	—	1	4	—	—	1	2	—	7	2	2	19	15.1
„ „ inactive to light	—	1	1	—	—	—	—	—	2	1	1	6	4.8
„ Ptosis ..	—	—	1	—	—	1	—	1	2	—	1	6	4.8
„ External ocular paresis	—	1	—	2	—	1	—	1	2	—	1	8	6.4
„ Changes in fundus ..	1	—	1	—	2	1	2	—	2	—	—	9	7.2
„ Dyschromotopsia ..	—	—	—	—	—	—	—	—	1	—	—	1	0.8
„ Nystagmus ..	1	1	—	—	—	—	—	—	4	—	1	7	5.6
Facial weakness ..	1	—	4	1	2	1	1	1	1	—	2	14	11.2
Paresis of tongue ..	—	—	—	1	2	—	2	—	1	1	—	7	5.6
Disturbance in swallowing ..	1	—	1	1	1	—	—	—	—	—	—	4	3.2
Respiratory paresis ..	—	—	—	2	—	—	—	—	—	—	—	2	1.6
Disturbance of sphincters ..	—	1	—	2	—	—	—	—	—	—	—	3	2.4
Giddiness ..	—	3	3	—	—	1	—	—	—	—	—	7	5.6
Headache ..	—	1	4	—	—	1	1	—	1	—	1	9	7.2
PHYSICAL SYMPTOMS—													
GENERAL.													
General condition, good ..	2	—	6	—	1	1	1	—	—	—	13	24	19.2
General condition, poor ..	1	—	2	—	2	—	4	—	2	—	25	36	28.8
Wasting ..	—	—	—	—	1	—	—	—	—	—	5	6	4.8
Feebleness ..	1	—	—	—	—	—	—	—	1	—	6	8	6.4
Anæmia ..	1	—	4	—	1	—	—	—	1	—	10	17	13.5
Cachexia ..	1	—	—	—	—	—	—	—	1	—	8	10	8
Jaundice ..	1	—	—	—	—	—	—	—	—	—	3	4	3.2
Evidence of cardiac feeble- ness or dilatation ..	3	—	3	—	2	1	2	1	2	—	24	38	30.2
Bronchitis and emphysema	3	—	1	—	1	—	2	1	2	—	10	20	8
Albuminuria ..	—	—	—	—	—	—	—	—	4	—	11	15	12
Abnormality in colour of urine ..	5	—	—	—	—	—	—	—	—	—	4	9	7.2
Constipation ..	3	—	—	—	—	—	—	—	—	—	3	6	4.8
Diarrhœa ..	—	1	—	—	—	—	1	—	1	—	5	8	6.4
DURATION OF DISEASE.													
Less than one year ..	3	8	4	5	1	1	1	1	8	5	5	42	33.6
More than one year ..	2	2	3	1	1	—	2	—	4	3	—	18	14.4
More than three years ..	—	3	1	—	—	—	—	1	3	—	—	8	6.4
COURSE—TERMINATION.													
Recovery ..	1	1	1	—	—	—	—	1	5	5	5	19	15.1
Amelioration ..	2	8	1	3	1	—	4	1	3	3	17	43	34.1
No change ..	—	1	1	1	—	—	1	—	3	1	9	17	13.5
Deterioration ..	—	—	1	—	—	—	—	—	1	—	—	2	1.6
Death ..	1	9	4	3	1	1	—	—	6	3	7	35	28

CASES.

GROUP A.

KORSAKOW'S DISEASE (POLYNEURITIC PSYCHOSIS). MENTAL
SYMPTOMS AND NEURITIS PRONOUNCED.*Case 1.*

A. D., aged 32. No occupation. Admitted June 17, 1903, complaining of a fainting fit.

History.—One brother died of hæmoptysis. No family or personal history of nervous or mental disorder to be obtained. Patient stoutly denies her habit, but her sister states that she is addicted to drink and simulates fainting fits to obtain it. Appetite poor. Memory has been failing. She has recently suffered from cramp and numbness and tingling in the feet.

State on admission. June 18, 1903.—A stout woman of alcoholic appearance. Nose and cheeks covered with dilated venules. Pulse 90, soft, regular. Tongue foul, coated and tremulous.

Mental symptoms.—Memory completely at fault for all recent events. Patient is garrulous and makes false statements. Mood, silly and childish. Speech, utterance thick and stumbling. Eyes nil.

Well marked extensor paralysis of both lower extremities; hyperæsthesia of the inner surface of left leg. Knee jerks diminished, left greater than right. All superficial reflexes increased. Muscular wasting. Edema of legs and ankles.

Chest.—Nil.

Abdomen.—Liver dulness extends below the costal margin, but its edge is difficult to make out by reason of the patient's obesity.

Course of case.—Patient was discharged a week after admission, her state being unaltered. During her stay she showed a tendency to have grandiose delusions.

Temperature subnormal throughout. Urine, 10·10, acid, contained phosphates and pus.

Case 2.

S. R., aged 49. Husband a fitter. Admitted November 3, 1903, for cough exhaustion and pains in the legs.

History.—Unreliable owing to the mental state of the patient.

but there seems to have been difficulty in walking for some time ; also pain and cramp in the legs. Recent failure of memory. Sleep poor. Anorexia and morning vomiting. Rheumatic pains in the joints. Alcoholic habit denied ; has taken whisky " by the doctor's orders." Catamenia have ceased lately. No serious illness in her life ; some of her labours were difficult. No history of nervous or mental disease in other members of her family.

State on admission.—Stout woman, lying partly propped up in bed. Respiration laboured, coughs occasionally. Typical alcoholic appearance ; bloated face with many dilated venules on the cheeks. Tongue clean. Pulse 90, soft, no thickening of the radial artery.

Nervous system. Mental symptoms.—There is complete loss of memory for all recent events and dates ; patient has even forgotten her own name. Sleep is poor and accompanied by vivid dreams, in which she seems to travel long distances. Mood facile, talkative, and occasionally anxious and fearful. Speech, no defect. Eyes, pupils equal and react normally to light and accommodation. Motor, no facial paresis. Paralysis of upper and lower extremities, chiefly affecting extensors ; patient cannot grasp with the thumb and fingers.

Sensation.—Hyperalgesia of legs ; no other qualitative alterations of sensation. Extreme tenderness to deep pressure of calf, muscles and ankles. General muscular tenderness of trunk.

Reflexes.—Both knee-jerks absent. No ankle clonus ; left supinator jerk absent ; plantar reflexes sluggish.

Nutrition.—No obvious muscular wasting ; skin mottled and atrophic.

Gait.—Weak and shuffling without obvious ataxia.

Special senses.—Unimpaired.

Heart.—Impulse diffuse ; reduplicated first sound followed by a systolic murmur at apex, not conducted outwards ; systolic murmur at base conducted towards the neck ; visible systolic pulsation of carotids.

Lungs.—Emphysema and scattered bronchial catarrh.

Abdomen.—No apparent enlargement of the liver ; large ventral hernia. Urine, sp. gr. 10·29, acid, concentrated, lithatic.

November 11, 1903.—Patient had an attack in which the limbs became suddenly rigid ; the temperature rose to over 100° F., and fell to normal in twenty-four hours ; she remained in a semi-conscious condition for several hours, during which she passed urine and fæces involuntarily.

November 12 and 13, 1903.—Takes no notice of her surroundings ; keeps up a muttering conversation.

November 16, 1903.—Incoherent and confused. Has a tactile illusion that the hands are covered with sticky material. Con-

stantly restless, searching in the bedclothes, trying to rub the sticky stuff off her fingers ; when disturbed she is rude and irritable ; seems also suspicious. Restlessness worse at night.

November 20, 1903.—Sleep improved. Incipient bed sore over the sacrum.

December 7, 1903.—Some improvement in mental state ; patient now talks rationally at times ; has no idea of time or place. Memory still defective. Neuritis still very severe.

December 10, 1903.—Again much confused ; has visual hallucinations, very restless ; temperature rises at night to 100° or more.

December 11, 1903.—Imagines she has a baby in the bed. Again tactile illusions based probably upon disturbance of sensation ; has a feeling as if gristle were slipping through her fingers. Objectively, there is evidence of loss of muscular sense ; patient unable to discriminate between her fingers with eyes closed, forgets everything in measure as she acquires it.—(Amnésie continue.)

December 23, 1903.—Memory still very poor ; completely disorientated ; visual hallucinations ; sees children in various parts of the room. Conducts a conversation more rationally. Mood occasionally facetious and jocular, but sometimes irritable and rude.

December 31, 1903.—Suspicious ; states that another patient has stolen her purse. Face wears a look of astonishment.

January 5, 1904.—Mood quieter ; still has visual hallucinations ; remembers to have made a false accusation against one of the other patients.

January 6, 1904.—Patient volunteered the statement this morning that she had just waken up ; everything up to now had seemed like a dream ; she now recognises her surroundings ; she is at Radnor Hall ! (where she was formerly a cook) ; she mistakes the nurses for persons who were concerned with the period of her life when she was at Radnor Hall. Occasionally, however, she is neither confused nor disorientated but fully recognises her surroundings. Mood varies with the state of the ideation ; when confused she is irritable, but when she is properly orientated she is placid and euphoric.

January 8, 1904.—Removed at the request of friends. Physical state and neuritis improved ; mental state unaltered.

Case 3.

J. McD., aged 57, auctioneer. Admitted February 26, 1902.

History.—No family history of nervous or mental disease. Jaundice twenty years before admission. Several fits in the immediate past, the details and exact dates of which he cannot remember. Syphilis denied ; he admits excessive drinking

(spirits). Has been unwell for two months; has had mental worry, and has suffered from sleeplessness; memory has been failing for eight months.

Condition on admission. January 27, 1902.—A well-nourished, rather senile individual. Restless and talkative; keeps muttering to himself; memory very defective; has completely forgotten the details of his admission to the hospital: he seems to have hallucinations of vision. Tongue, sloughy ulcer on left border. Pulse, 100. Heart, action feeble, pulmonary second sound increased, soft systolic murmur at apex, not conducted outwards. Lungs, scattered rhonchus. Liver dulness extends one inch below the costal margin. Knee-jerks diminished. Legs wasted. Urine, sp. gr. 10·10, contains a trace of albumen.

February 28, 1902.—After sleep, some improvement in mental condition.

March 4, 1902.—Discharged.

June 9, 1904.—Readmitted.

He states that he has had several fits since last admission, and that he has had an attack of sunstroke, also more or less mental trouble. These statements are unreliable because of his mental condition.

Condition on re-admission. June 10, 1904.—A spare man, sandy hair and beard turning grey; senile appearance; fairly vigorous. Tongue, clean. Pulse, regular, arterial tension low. Heart, apical systolic murmur not conducted outwards. Lungs, nil. Abdomen, the liver is much enlarged, smooth and firm to the touch. Some distension, possibly due to ascites.

Mental state.—Patient excitable, restless and talkative. Mood facile, obliging and facetious. He seems to understand what is said to him, but his answers are sometimes irrelevant, and he wanders at random from one train of thought to another. Memory for events and dates in the far past precise and accurate; on the other hand, he has great difficulty in remembering what has occurred recently. No failure in immediate reproduction. No disorientation.

Eyes.—Pupils unequal and react rather sluggishly to light. Tremor of tongue and facial muscles, also of hands; tremor increased by effort. No paralysis of extremities; movements ataxic. Tactile and painful sensations are discriminated and properly localised, but there is hypo-æsthesia of the skin of the trunk below a transverse line 2 inches above the umbilicus; this is borne out by the æsthesiometer. Hypo-algesia of external surfaces of thighs; patchy hyper-algesia of legs; soles of the feet hyper-æsthetic. All the foregoing sensory anomalies vary much from time to time. No deep tenderness on pressure.

Reflexes.—Knee-jerks absent.

Nutrition.—General muscular wasting; skin atrophic.

June 11, 1904.—Was delirious during the night. Urine, low specific gravity, contains albumen.

The mental state continued unaltered; delirium for the first ten nights.

June 29, 1904.—Discharged.

Case 4.

J. W., aged 41, mental nurse. Admitted August 28, 1904, for languor, pain in the chest and shortness of breath.

History.—Both parents and a brother addicted to drink; a brother has delusions of persecution. A relative states that the patient has been an habitual drunkard (spirits) for years. Five months before admission, it was noticed that she asked the same question repeatedly; she became excitable and emotional, and used to weep for no apparent reason; she also became suspicious, and thought people were plotting against her. Sleep has been good. "Sleeping (!) very well both day and night." She has suffered for a long time from indigestion and morning vomiting, and is said to have had hæmatemesis. Patient's own account of her past history was quite unreliable.

State on admission. August 24, 1904.—Pale and anæmic, extremely restless, picks constantly at the bed clothes, and talks incoherently. Tongue, tremulous and coated. Pulse, 100. Heart sounds feeble, irregular and intermittent; præcordial dulness increased to the right. Lungs, apparently normal. Liver, enlarged and tender; edge felt three inches below costal margin.

Nervous system.—Well marked extensor paralysis of legs. Knee-jerks absent. Tenderness on deep pressure of muscles of calves. Patchy anæsthesia of legs. Superficial reflexes brisk.

Mental condition.—Patient confused; has lost all memory for recent events, whilst apparently able to remember all that occurred in the far past. At night time she seems frightened, and makes frequent attempts to get out of bed. She confabulates; has no idea of where she is or of the present time. Quite cleanly in her personal habits.

Tremor of hands and tongue. Temperature 99° F., rising to 100° at night. Urine normal.

August 30, 1904.—Restless night; made frequent attempts to get out of bed; much confused.

September 6, 1904.—No improvement in mental condition. Heart's action feeble; systolic murmur at apex, rhythm irregular. Legs are rigidly flexed, and attempts at extension cause great pain.

September 8, 1904.—Mental condition somewhat improved, but patient is still completely disorientated in her surroundings; she has no idea of the day of the month or of the month of

the year. Confabulates constantly, story always of her past life. Attention fugitive. Mood, placid, self-laudatory: "If I hadn't worked so hard I shouldn't be so ill." She weeps on the slightest provocation.

September 11, 1904.—Patient reported to be excited at night; tried to get out of bed. At times rational, at times incoherent. Sensation, tested by æsthesiometer, normal. Mood alternates rapidly from depression to gaiety. Facial expression staring and frightened. Complete loss of memory for all events immediately after they have occurred. Disorientated. Mistakes the ward sister for an old acquaintance. She remembers having received a letter from her sister a few days ago, but cannot remember any of its contents. Denies her habit.

September 14, 1904.—No change in mental condition; she is more disorientated at some times than at others. Neuritis still severe.

September 9, 1904.—No change.

September 29, 1904.—Sudden severe melæna, after which she was very collapsed.

October 10, 1904.—Some improvement of mental state, but there is still disorientation and loss of memory. Temperature normal or sub-normal during the day, raised to 99° or 100° F. at night. Neuritis was still severe when she left the hospital.

Case 5.

C. S., aged 42, ex-lady's maid; husband a butler. Admitted October 5, 1904.

History.—Patient's own account unreliable owing to mental condition. She was attended by a doctor in May, 1903, for bronchitis, epistaxis and "congestion of the liver." She was then told to relinquish her habit of spirit-drinking, but she did not do so. In July, 1903, she had a very severe attack of diarrhœa. During 1903 she lost 3 stones in weight. Patient states that numbness and tingling have been present in the legs for more than a year; morning vomiting has also been constant during the year before admission. She stoutly denies her habit. No history of alcoholism or nervous or mental disease in other members of her family.

State on admission. October 6, 1904.—Patient thin and wasted; complexion sallow and earthy; face puffy, leashes of dilated venules on the nose and cheeks. Pulse 112, feeble. Chest, some impairment of resonance at the apices of the lungs; no cough or expectoration. Liver enlarged; dulness extends from level of fifth costal cartilage downwards to 2 inches below the costal margin; hard to the touch, edge sharp and easily felt. No ascites. Urine, acid, sp. gr. 10·20, contains a trace of albumen.

Mental condition.—Mood placid and gay ; she is facile, ingratiating and desirous of making a good impression. Her conversation betrays no disturbance of ideation on the surface, and might easily convince a casual observer that there was nothing amiss. She is, however, incapable of pursuing one train of thought for longer than a few seconds, and wanders off into reminiscences of her past life which are obviously false. The memory is very defective for recent events, but this might also escape observation, because she wilfully conceals the defect by substituting pseudo-reminiscences. She is completely disorientated ; thinks that yesterday (Wednesday) was Sunday ; that the day of the month (October 6) is December 25, and that she is in St. Thomas' Hospital (she is actually in St. George's Hospital). She also mistakes the nurses for old acquaintances. Sleep fair ; no visual hallucinations, but her dreams are vivid, of a pleasant nature, and connected with travel. Speech, no impairment. Eyes (pupils dilated by homatropin), no external ocular paralysis ; fundi normal. Motor : tremor of the circum-oral muscles, brought out on emotion ; bi-lateral wrist drop ; extensors of fingers almost completely paralysed, flexors less so ; intrinsic muscles of the thumb weak. She cannot raise her legs from the bed ; any attempt to move them passively causes intense pain. Knees flexed.

Sensation.—Diminished sensibility to pain and tactile stimuli in fingers. By the æsthesiometer two points discriminated.

	Right	Left	Normal.
On palmar surface of terminal phalanx	12 mm.	30 mm.	3 mm.
On fore-arm	85 „	45 „	30 „
On skin over malar bones ...	8 „	5 „	11 „

In the legs both painful and tactile sensations are delayed, but they are discriminated one from the other ; heat and cold not distinguished on soles of feet. Extreme tenderness to deep pressure of calves and fore-arm muscles.

Reflexes.—Knee-jerks absent ; superficial reflexes sluggish.

Nutrition.—Much muscular wasting ; œdema of ankles and dorsum of feet.

Sphincters.—Urine passed involuntarily in bed. Incoördination of small movements of the hands ; some intention tremor.

October 7, 1904.—Mental state worse ; more confusion. Sensory disturbance in legs more marked.

October 10, 1904.—Patient confabulates constantly. Stated that she had eaten a pear for lunch (false) ; that her husband had just visited her (false). Has no idea of the day of the month, fancies herself in St. Bartholomew's Hospital. Mood euphoric ; occasionally wet and dirty.

October 24, 1904.—Some improvement in neuritis. Mentally, still disorientated. Mood, generally cheerful, but sometimes restless and anxious ; wants to go out and buy Christmas (!) presents.

November 4, 1904.—No alteration. Rational only occasionally.

November 8, 1904.—No improvement; still has no idea of time or place; states that she gets up and goes out every day (false). Mood cheerful on the whole.

December 19, 1904.—Physical condition improving; more power in legs. Mental state improved; she now realises her surroundings. Memory still extremely poor.

December 20, 1904.—Removed from hospital at the request of friends.

GROUP B.

KORSAKOW'S DISEASE (POLYNEURITIC PSYCHOSIS).

MENTAL SYMPTOMS PRONOUNCED; NEURITIS SLIGHT OR ABSENT.

Case 1.

E. C., aged about 60 years. Needlewoman. Admitted June 6, 1904. On the morning of day of admission patient had an attack of unconsciousness and fell off the chair on which she was sitting to the ground. When admitted she was still unconscious; pupils were dilated and inactive to light. While being conveyed to the ward she had a typical epileptic fit with clonic contractions of the limbs; she also passed her urine beneath her.

State (June 7, 1904).—A spare woman of senile appearance; dilated venules on the nose and cheeks; lies in the cerebral position with the thighs and legs flexed.

Mental condition.—Patient is now conscious; she is irritable and resents disturbance; occasionally noisy and incoherent. No memory for recent events. Speech, sluggish. Pupils, unequal and inactive to light and accommodation; conjugate movements of the eyes performed normally. No facial paralysis; grasp of both hands weak; no paralysis of lower extremities. Sensory: all stimuli perceived, but reaction delayed (twenty seconds). Calves seem a little tender to deep pressure. Reflexes: knee-jerks exaggerated. Superficial reflexes exaggerated. Tongue protruded mesially; no tremor. Heart action feeble; sounds poor; reduplication of first sound at apex. Pulse 96, feeble, regular; low arterial tension. Lungs, nil. Abdomen nil. No signs of enlargement of the liver. Urine, 10·20, acid, no albumen or sugar.

June 8, 1904.—Friends state that she has been intemperate for years; she has never had an epileptic fit before the present attack. Patient is still dazed and somnolent. Pupils still unequal and sluggish to light. No squint or nystagmus. Limbs all rather rigid.

June 9, 1904.—More rational. When she sits up feels giddy and tends to fall to the right.

June 10, 1904.—Patient on the whole more rational but at times gives incoherent replies. Disorientation is complete; she has no idea of time or place; can remember no dates in the immediate past. Confabulation; states that she has just arrived by omnibus (false). She believes she is in a hospital, but does not know which; mistakes the identity of persons and addresses the nurses as her intimate friends. Memory for events in the far past quite clear. Loss of memory seems to extend to the events of a few days before the onset of present illness; suspicious; imagines she is being ridiculed and made fun of. Mood querulous, but at the same time facetious and ironical. Skin of abdomen hyperæsthetic. Knee-jerks could not be obtained. She still shrinks if deep pressure is exerted on the muscles of the calves.

June 20, 1904.—Sensation (tested by æsthiometer) somewhat defective in fingers. Memory very defective; cannot remember the name of the hospital or of the ward. Mood, irritable and depressed.

June 23, 1904.—Conduct silly; tries to leave her bed; throws cups and plates on the floor. Pupils still unequal but react to light. Sensation objectively normal. Fundi normal. Knee-jerks absent. Cries out with pain if legs are handled. Speech normal.

July 14, 1904.—Apathetic and more somnolent. Takes no notice of her surroundings. When addressed talks irrationally about her symptoms. Occasionally emotional and lachrymose. Confabulates constantly; articulation indistinct; Passed her urine beneath her.

July 18, 1904.—Removed to the infirmary.

Case 2.

C. M., aged 58, hairdresser. Admitted August 8, 1902.

Patient brought to the hospital in the early morning in a partially unconscious condition. The policeman who brought him to hospital stated that he was well known as an idler and a drunkard. Pupils contracted. After the stomach had been pumped out he recovered consciousness sufficiently to answer questions. Stomach contents did not smell of alcohol. Articulation thick: no facial paralysis or paralysis of limbs. As he continued to be drowsy, the idea was entertained that he was under the influence of morphia and he was therefore walked up and down, but subsequently left to rest.

Urine, 10·16, acid, no albumen. Thoracic and abdominal viscera normal. Edema of legs.

August 19, 1902.—*Mental state*.—Stuporose: when sufficiently roused answers questions rationally at first, but lapses into somno-

lence and incoherence. Knee jerks active. No paralysis or rigidity; occasional twitching of the limbs on the left side. Pupils still small; react to light.

August 20, 1902. Less drowsy; articulation less thick.

August 24, 1902.—Last night excited; tried to leave his bed, but soon quieted down.

August 25, 1902.—Mood apathetic.

August 26, 1902.—Occasionally very excited; seems to have hallucinations of vision. Always more excited at night.

August 28, 1902.—Confabulates; says he has been out in the yard to-day but was obliged to come back to the ward because of pains in his legs (false).

August 28, 1902.—Quiet and apathetic by day; excited and restless at night; complains of headache.

September 4, 1902.—Confabulates continually; very excited and restless at night.

September 16, 1902.—Mental condition much the same. He accused the ward sister of stealing two suits of clothes and a silk hat (he came to the hospital practically in rags). Removed to the infirmary.

Case 3.

J. McC., aged 39, admitted September 17, 1902. Found wandering aimlessly in a dazed condition in Hyde Park.

On admission.—Seemed rather cold; pulse feeble. Could give no rational account of himself. Disorientated in his surroundings; did not know he had been brought to the hospital, but denied absolutely having been brought there by a policeman. A few minutes later, when asked—"Where are you?" replied, "in a model lodging house." Extremely stupid and dazed; mutters incoherently. Said that the day before admission he had had much vomiting and diarrhoea; admitted to recent heavy drinking; denied syphilis.

Nervous system.—Inward movement of the left eye deficient. Well marked lateral nystagmus: slight ptosis of left eye. All these symptoms disappeared with the exception of slight nystagmus by the afternoon. General tremor. Knee-jerks absent. Superficial reflexes all very brisk. Heart's action feeble and irregular: impulse flabby, first sound insufficient; pulse 112.

September 17, 1902.—Mental condition slightly improved; still very listless and apathetic. Ophthalmic surgeon reports "vertical movements very deficient; no power of convergence."

September 23, 1902.—Discharged: mental and physical condition improved.

Case 4.

I. O., aged 50, governess. Admitted August 14th, 1904, for purpura.

History.—Bleeding from mucous membranes, especially from gums, for two years off and on: frequent attacks of epistaxis. Often has purpuric rashes on the skin. Lately has suffered from cramp in the legs and pains in the limbs. Catamenia ceased at age of 38. Patient used to keep a school but has recently been out of employment and in straitened circumstances.

State on admission.—Pale complexion: alcoholic appearance. Muscles flabby, conjunctivæ icteric: the skin is covered with a purpuric rash, principally on extremities. Rash varies from pin point spots to areas $3\frac{1}{2}$ inches in diameter.

Mental symptoms.—Memory impaired for recent events. Mood, fussy and garrulous. Confabulates and gives a confused account of her history. General fine tremor. Knee-jerks present.

August 20, 1904.—Complains of numbness and tingling of feet.

August 21, 1904.—Discharged.

Case 5.

A. C., aged 34, publican. Admitted October 5, 1903, in a condition of delirium tremens.

History.—His wife states that he has for some time been depressed and irritable, over-anxious about business: memory has been failing rapidly; he mislays objects, forgets immediately where he has put them. On the night before admission he had an auditory hallucination; imagined he heard a brass band; sleepless for many nights. He is not often the worse for drink, but habitually drinks freely in the course of business.

State on admission.—Well built man; healthy appearance. Mental condition practically one of delirium tremens; exceedingly restless and tremulous; has visual hallucinations of animals. Talks constantly and evidently imagines that he is serving drinks behind the bar. Attention can be held only for a few moments, after which he at once lapses into delirium.

Eyes, nil. Speech, nil. Tongue protruded steadily: fine tremor of lips and hands. Knee-jerks present. No paralysis. Temperature raised.

Course of case.—Delirium ceased in about twenty-four hours, but until October 19, though quiet, he was completely disorientated in his surroundings and had no idea of time. Memory completely lost for all details of immediate past. At night the delirium returned with visual hallucinations.

October 21, 1903.—Removed by his wife against advice.

Case 6.

I. K., aged 45. Coachman's wife. Admitted August 26, 1904.

History.—Patient had a "faint" in the street, her legs seemed suddenly to give way beneath her. Morning vomiting for some time past: she drinks beer for breakfast, and spirits occasionally. No family history of alcoholism or nervous disease.

On admission.—Very tremulous. Memory for recent events defective. Confabulates and makes confused statements. At night, visual hallucinations and temperature rises to 100° F. Pupils, equal, react normally to light and accommodation. Muscles of calves tender to deep pressure: no paralysis or objective disturbance of sensation. Knee-jerks exaggerated. Urine contains albumen.

August 30.—Less tremor: sleeps better; not so much excitement at night. Memory still defective.

September 3.—Discharged. Condition improved.

Case 7.

A. W., aged 51, solicitor. Admitted March 5, 1902, in an unconscious condition.

History.—Patient had felt "queer in the head" for two days; his manner seemed peculiar and his speech imperfect. On the morning of admission he seemed to have lost his memory; speech still more difficult, after which he sank into a state of unconsciousness. Patient is addicted to drink and there is a pronounced history of nervous disease in other members of his family: his father died of apoplexy, his mother of general paralysis and tabes. Two aunts on his father's side also died of apoplexy.

Present state.—March 6, 1902. Stout man; lies unconscious in bed, breathing stertorous at times. Pupils, under the influence of homatropin, corneal reflex present. Fundi normal. Temperature 103°. Pulse 120, soft; respiration rate 30. Breath has no characteristic odour. Heart, aortic second sound accentuated. Lungs, normal. Abdomen, normal. Urine, acid, 10·22, no albumen or sugar. Both fore-arms are rigid and flexed; fingers strongly flexed into the palms. Arms adducted; both legs rigidly flexed. No evidence of paralysis. No convulsions. Knee-jerks diminished: has lost control over sphincters.

March 7, 1902.—Patient has regained consciousness and breathes naturally. When roused, he stares vacantly about him and seems to have no idea of his surroundings. He does not answer questions. Rigidity has disappeared.

March 10, 1902.—Answers questions rationally at times; is disorientated; states that he knows where he is, "in Black-

heath (!)." In the middle of a sentence he stops and repeats one syllable indefinitely, then lapses into silence. When asked to write the day of the week he writes it twice, thus: "Monday, Monday." He is restless and excited at night and requires a male attendant.

March 20, 1902.—Some improvement in mental condition: still confabulates and makes false statements; restless at night.

March 21, 1902.—Discharged. Temperature fell to normal the first day and remained so.

GROUP C.

KORSAKOW'S DISEASE (POLYNEURITIC PSYCHOSIS). MENTAL SYMPTOMS SLIGHT; NEURITIS PRONOUNCED.

Case 1.

F. B., aged 36. Husband a mason. Admitted February 12, 1903, for cramp in the legs and numbness and tingling in the feet.

History.—Uncle and two aunts on father's side died insane. Also epilepsy in another member of the family. Morning vomiting and indigestion for some time. Symptoms of neuritis gradually coming on for seven months; began with cramp, numbness and tingling of feet and legs. She also began to trip over objects when walking and her knees occasionally gave way beneath her.

State on admission.—Stout woman with characteristic bloated face. There is a want of tone about the facial muscles which gives the face an expressionless look. Tongue, tremulous. Neuritis well marked. Extensor paralysis of both feet. Knee-jerks absent. Liver, much enlarged and tender. Mental symptoms were confined to an alteration of mood; she was silly and talkative and abnormally jovial and facetious. No obvious impairment of memory or disorientation.

Case 2.

A. T., aged 42. Husband a coachbuilder. Admitted October 29, 1903, complaining of cramp in the calves of the legs.

History.—Symptoms of neuritis began nine months before admission with cramp; there has been paræsthesia and difficulty in walking. When she stoops, she is afraid to raise herself up for fear of falling. She has noticed no alteration of the state of her mind. Hæmatemesis ten years before admission; no recent dyspepsia or vomiting in the morning. Catamenia ceased two months before admission. No family history of nervous or mental disease.

State on admission.—Dissolute, alcoholic appearance; dilated venules on the cheeks; eyes suffused.

Mental condition.—Mood unduly cheerful. She is at times talkative and silly, and at times apathetic and listless; the attention is fugitive. The absolute denial of her habit is typical. There is no pseudo-reminiscence or loss of memory and the patient is properly orientated.

Eyes, nil. Speech slurring and indistinct. The symptoms of neuritis were severe; extensor paresis of both extremities, upper and lower, objective alterations of sensation; absent knee-jerks.

Patient had some incontinence of urine, which was attributed to laziness; it disappeared when dismissal from the hospital was threatened.

GROUP D.

ALCOHOLISM WITH HYSTERICAL SYMPTOMS.

Case 1.

(Mental symptoms were in many respects like those of Korsakow's disease).

M. A. C., aged about 45, lodging-house keeper. Admitted November 10, 1903.

History.—Patient felt quite well on morning of admission. She came up to town to bank some money, and while getting into an omnibus at Victoria Station, she was jostled and found that her purse had been stolen. The sum of money was a large one and the loss of it caused her considerable anxiety. She remembers going back into the station to despatch a telegram, but afterwards her mind became a blank until she found herself in the hospital. Lately she has had business worry; she has felt at times "queer in the head," has forgotten where she has placed objects. She denies excess in alcohol. Always nervous when a child, and had emotional attacks. Brother epileptic. Aunt insane. Her relations subsequently reported that patient had been hysterical since the age of 18, had never had "fits," but had recently been addicted to drink.

State on admission.—November 10, 1903.—Very stout woman, face blotchy and bloated. Head a little microcephalic.

Mental condition.—Patient has completely lost her memory. Every fact of her past is, as it were, completely blotted out; she cannot even recollect her own name, and it is therefore impossible to communicate with her friends. She believes she has come from somewhere by train, but cannot say from where. There is also complete loss of the sense of her own personality. When shown her hands she said: "These are not my hands, my hands have gone with the rest of me; they do not exist; I wish I

could find them. I wish I could find myself." She is object blind and word blind ; when a fork was presented to her she tried to comb her hair with it, obviously not recognising its use. There is no auditory aphasia and she appears to understand most of what is said to her. When asked to put out her tongue she replied : " I would, but I don't know where it is " (sense of negation of the personality). She cannot, however, understand nouns. Thus, when a fork was shown to her and I said "This is a fork," she did not understand the word "fork." A moment after, however, when I said "Where do you put the forks," she replied at once, "The silver ones in the dining room, the common ones in the kitchen." The defect is, therefore, not constant. She can write correctly to dictation anything except proper nouns, for which the auditory memory is defective. Patient's behaviour is perfectly rational and her aphasia is only present when she has to make a conscious effort.

Speech, no dysarthria. Eyes, pupils act normally to light and accommodation and are equal. Visual fields concentrically contracted. Motor, no facial paralysis ; grasp weak on both sides, also opposition of thumb to fingers. Sensation, almost complete anæsthesia and analgesia everywhere, but there are hyperæsthetic areas on the abdomen, soles of the feet, and on the outer sides of the thighs. The state of the objective sensory disturbance varies much at different times. Reflexes : knee-jerks exaggerated. Plantar reflex active, flexor response. Nutrition, no obvious muscular wasting. Coördination interfered with by the sense of personal negation. Thus, when asked to place the forefinger on the tip of the nose with eyes closed, she could not do so. When told to try with her eyes open, she failed also, and excused herself by saying "I cannot do so ; my nose is lost." Gait, astasia, abasia. Heart and lungs, normal. Pulse 112. Liver much enlarged. Urine contains a trace of albumen.

November 11, 1903.—Memory returning ; remembers her name and address. She states that she found them by praying in the dark. Sensation returning ; to-day complete left hemianæsthesia, also stocking and glove anæsthesia of right side ; visual fields still contracted. In the evening patient had a typical attack of hysteria major with opisthotonos.

November 11, 1903.—Fields of vision wider. Patient, who has hitherto been placid and apathetic, now is irritable and discontented, hemianæsthesia less complete ; hands and feet still anæsthetic.

November 16, 1903.—Fields of vision still wider. Memory completely restored. Knee-jerks active. Still some anæsthesia of left side. Mind quite normal. Discharged.

Case 2.—This case is quoted to illustrate the difficulty which may arise in distinguishing the symptoms of functional disease from those of neuritis. Neuritis was undoubtedly present, but the mental symptoms were of an hysterical nature.

G. S., aged 48. Commercial traveller. Admitted February 10, 1904, complaining of inability to walk and pain in the left leg and arm.

History.—Patient comes from a nervous stock. His father was an alcoholic and his mother died of a nervous affection. Patient has for a long time led a dissolute life; he has been habitually intemperate and has been in more than one inebriate asylum; he contracted syphilis four years before admission. Two years ago he was in St. Thomas's Hospital with an attack of complete left hemianæsthesia. Rheumatic fever and a head injury in his youth. The present illness began six months ago; while out for a walk he suddenly lost all power in his legs and fell; he had to be taken home in a cart. Since then he has been laid up; he has had much pain, "rheumatic," in the shoulders and legs. Memory has been failing for some time, especially that for proper names. On the evening after admission patient had an attack in which he became suddenly rigid for a few minutes, also during sleep the right hand assumed the pose of a hand crippled by osteo-arthritis. This had disappeared by the morning (auto-suggestion).

State on admission (February 11, 1904).—Bloated alcoholic facies; cheeks and nose covered with dilated venules; tongue furred and tremulous. He continually eructates loudly and noisily. Pulse 88, regular, tension low.

Mental condition.—He answers questions clearly and rationally; there is some slight difficulty in recollecting recent facts. Mood jovial, facetious; tendency to make jokes.

Eyes, pupils sluggish to light; react normally to accommodation. No paralysis to external ocular muscles; no nystagmus; visual fields much contracted concentrically. Motor: no facial paralysis. Grasp weak on both sides, but no paralysis of either arms or legs. The right leg is spastic, and on the slightest touch is thrown into pseudo-clonus; spasm can be easily overcome. Sensation: generalised diminution of sensibility to all forms of stimuli, most pronounced in hands and arms, where heat and cold can also not be distinguished. Much tenderness of the calves of the legs on deep pressure. Reflexes: left knee-jerk about normal; right not to be estimated because of spasm; supinator jerks active. All superficial reflexes present and about normal. Coördination and gait: when patient tries to stand he trembles violently all over, but does not sway or fall. He can walk when urged to do so, but right foot drags; Romberg's sign absent. Vaso-motor: the extremities,

and especially the hands, are cold, rigid and rather blue. Some œdema of shins. Heart: action occasionally excited; sounds weak; præcordial dulness increased. Lungs: emphysematous. Liver: enlarged.

Patient discharged two days after admission.

GROUP E.

CASES PRESENTING DIFFICULTIES IN DIAGNOSIS BETWEEN KORSAKOW'S DISEASE AND OTHER AFFECTIONS.

Case 1.

(Diagnosed as General Paralysis).

J. H., aged 37. Does odd jobs. Admitted February 25, 1902.

History.—No accurate history to be obtained because of the patient's mental condition.

State on admission.—Alcoholic appearance; skin subicteric.

Mind.—The mental faculties are dulled. Sometimes he does not reply to questions, at others he answers incoherently. No reliance can be placed on his statements. Complains of feeling choked, but is quite obviously not in any distress.

Nervous system.—Knee-jerks not obtained. Pupils unequal, rather sluggish to light. Calves not tender. Tremor of hands and tongue. Speech, normal. Heart and lungs, normal. Liver, much enlarged, hard; edge felt half way between umbilicus and costal margin.

February 28, 1902.—Very uproarious and excited early in the morning; later grows quieter.

March 10, 1902.—Mind now quite clear. Discharged to infirmary.

Case 2.—In this case the diagnosis for some time lay between General Paralysis and Korsakow's Disease.

E. R., aged 40, housemaid. Admitted November 4, 1903.

History.—The day before admission the patient was found wandering in the street in insufficient attire. Her sister stated that she had been extremely irritable and "queer in the head" for six months. No history of nervous or mental disease in any other members of her family. Patient herself has been intemperate in the past.

State on admission.—Moderate nutrition; complexion sallow. The face has a vacant look; she takes no notice of her surroundings, and appears to be demented. Tongue, moist, tremulous. Pulse, 96, full, regular; radial artery tortuous and thickened. Temperature, sub-normal. Heart: aortic 2nd sound accentuated

and ringing, otherwise normal. Lungs: normal. Liver not enlarged.

Nervous system.—Pupils unequal, left pupil sluggish to light. Knee-jerks, right normal, left exaggerated. No paralysis. Slight general muscular rigidity.

Urine, 10·20, clear, yellow, no albumen.

Mental condition.—The patient is either demented or merely stuporose. She takes no notice of her surroundings, but mutters constantly to herself. She replies to questions, but her remarks are incoherent. The speech is hesitating, and there is facial tremor. She appears to have difficulty in finding the right words to fit her ideas.

November 7, 1903.—Mental condition much the same; she is incoherent, and does not realise her surroundings. Sleeps badly.

November 8, 1903.—Patient stated that she had had a letter from the King, presenting her with a silver-mounted motor car. Mutters to herself; speech rather slurring. When she tries to write her writing is tremulous.

November 11, 1903.—General condition deteriorating; she is much weaker, and is becoming emaciated. Tongue dry; passes everything beneath her.

November 12, 1903.—Worse; face thinner; expression anxious. Abdomen distended and tender. Vomited.

November 13, 1903.—Bowels opened by castor oil; all distension has disappeared.

November 14, 1903.—Slept better. Mood gay and jovial. Laughs frequently at very little; inclined to be noisy.

November 16, 1903.—Nurse reports that the state of the patient's mind varies greatly from time to time. At times she appears to be quite demented, but at times she suddenly becomes herself, and converses quite rationally.

November 18, 1903.—Excited and noisy at night. Seems to have visual hallucinations. By day, quiet and euphoric. No signs of multiple neuritis; calves not tender; muscles look wasted, but contract to faradic current. Knee-jerks are, however, absent.

November 20, 1903.—General condition much improved. Tongue clean and moist. Mentally gay and lighthearted; sings and talks to herself.

November 24, 1903.—Removed to the infirmary.

Case 3.—*A case of alcoholic neuritis in which the mental symptoms were confined to an alteration of mood. The pupillary disturbance gave rise to a diagnosis of tabes dorsalis with commencing general paralysis.*

L. B., aged 33. Admitted April 29, 1903, for pains in the legs and feet, stiffness in the right hand, and general lassitude and fatigue.

History.—No history of nervous or mental disease in other members of her family. Appetite has been failing recently. Habit denied, except whisky occasionally. For the last two years occasional pain and sensations of numbness and tingling in the feet and hands. Memory has been failing. For the last five weeks the legs have been growing weak and her gait has been staggering. Ankles have been swollen. Feeling of dulness and pressure on the head.

State on admission.—Face puffy; obliteration of the nasolabial folds due to slight facial paresis. Complexion blotchy and pitted by smallpox. Appearance suggests alcoholism. Tongue, furred, moist and tremulous.

Nervous system.—Mental: Patient is emotional; laughs and weeps for insufficient reason; at other times she is apathetic and listless. No objective evidence of loss of memory. Speech, normal; she states that she sometimes has difficulty in speaking. Eyes, pupils unequal; left larger than right, and irregular in shape. Haze on left lens. Vision fair; she can read ordinary type, but states that after reading for a short time the words become blurred. No plus tension of the globes. No nystagmus, squint or paralysis of the external ocular muscles. Motor: tremor of the tongue and facial muscles. Some extensor paralysis of lower extremities; cannot dorsiflex the feet strongly. Sensation: hyperæsthesia of the back as far down as the middle of the sacrum; cannot distinguish between painful and tactile stimuli on the legs, thighs and buttocks; arms also hypoalgesic. No deep muscular tenderness of legs. Vaso-motor, "Tâche cérébrale." Reflexes: knee-jerks exaggerated; plantar reflexes very active. Gait: great unsteadiness.

Romberg's sign present. Sphincters, nil.

May 5, 1903.—Pupils unequal; left larger than right; react slightly to light and accommodation.

May 9, 1903.—Complete inactivity of the pupils to both light and accommodation. Ophthalmic surgeon reports, "Fundi normal."

May 11, 1903.—Yesterday the left pupil did not react to light or accommodation; to-day both react normally.

May 5, 1903.—Left pupil reacts to accommodation only; right to both light and accommodation.

Case 4.—A case in which the diagnosis lay between alcoholic neuritis and tabes dorsalis. Mental symptoms confined to a slight alteration of mood.

M. S., aged 31, housemaid. Admitted November 24, 1903, complaining of pain in the stomach, head and back, and numbness in the feet.

History.—Onset of illness gradual, with feelings of weakness, lassitude and indigestion. Some weeks ago, sudden sharp pains in both iliac regions; lately the iliac crests have seemed tender. Several attacks of crampy pain in the epigastric region. She has only vomited once, after some medicine, but often feels sick in the morning. Now and again sharp pain in the sacral region, also darting pains in the limbs. Lately, a little difficulty in walking, and a feeling in the feet as if she were walking on soft material. She often has cramp in the calves. Bowels constipated; no difficulty in micturition.

State on admission.—Stout woman; face suffused; tongue flabby and tremulous. Mental: mood abnormally facile and childish. (Suggests an early stage of polyneuritic psychosis.) Speech, nil. Facial tremor and fine tremor of the hands. No paralysis. Sensation: no objective alteration. Reflexes: knee-jerks absent even on reinforcement; also tendo-Achillis jerk. Superficial reflexes, normal. Coördination: no Rombergism. Unsteadiness if she attempts to "toe and heel" one plank of the flooring. No steppage. Pupils, contracted and unequal; right larger than left. Definite Argyll-Robertson phenomenon. Sphincters normal.

Summary.

In favour of tabes.

1. Argyll-Robertson Pupil.
2. History suggesting lightning pains and gastric crises.
3. Unsteadiness of gait.
4. Absent knee-jerk.

In favour of alcoholic neuritis.

1. Tremor.
2. Facies.
3. Mood.
4. Tenderness of calves.
5. History of morning sickness.
6. Condition of heart (*vide infra*.)

Heart: action feeble; impulse flabby; first sound short and reduplicated. Lungs, nil. Stomach, dilated. Liver, no enlargement. Urine phosphatic.

December 1, 1903.—Mood varies between despondency and cheerfulness; patient complains continually of pain in both iliac regions radiating to thighs. Gynæcological examination revealed chronic pelvic peritonitis with fixation and retroflexion of the uterus.

In the following two cases of chronic alcoholism the mental symptoms were explained by tuberculous meningitis, unsuspected during life but revealed at the autopsy.

Case 5.

H. P., aged 34, publican. Admitted on October 19, 1903, in a semi-conscious state.

History.—The practitioner who has been attending him states that he had an epileptiform attack a fortnight before admission; in his opinion the patient's condition is due to drink. Patient's brother states that he has had several previous attacks of a similar nature. Patient is a hard drinker.

October 20, 1903.—Patient has to a certain extent regained consciousness. When asked to give his name he mutters it in a low voice; also puts out his tongue when requested. When left to himself, he mutters constantly, and his behaviour suggests that he is the subject of visual hallucination.

Eyes: pupils react to light and accommodation; convergence, normal. All eye movements normally performed; no strabismus. Speech, thick and unintelligible. No tremor; no paralysis. Pulse, 96; radial artery thickened. Heart, nil. Lungs, scattered ronchus. Abdomen, nil. Bowels closed; has passed no urine. Alcoholic facies; complexion blotchy; dilated venules on cheeks.

October 21, 1903.—Temperature 100°. Still muttering delirium and visual hallucination. Restlessness and carphologia.

October 22, 1903.—Sudden attack of complete left hemiplegia and hemianæsthesia. Temperature 101° F. Left arm rigid, but left leg flaccid. Conjugate deviation to the right. Knee-jerks equal and normal in intensity. Pupils react to light; corneal reflex absent on left side. Patient is delirious and tries to catch imaginary objects in the air.

October 23, 1903.—Died. State unchanged.

At the autopsy there was pronounced tuberculous meningitis.

Case 6.

W. N., aged 43, club waiter. Admitted July 6, 1903, complaining of loss of power in the legs.

History.—Has noticed weakness of the legs in going upstairs for some time past. No morning vomiting. Admits to habitual excess in alcohol. Syphilis in the past.

State on admission.—Fat, flabby-looking man, tremulous and restless. Appearance of chronic alcoholism. Pulse, 88; radial artery thickened; low arterial tension. Heart sounds weak and distant. Lungs, nil. No enlargement of the liver.

Nervous system.—Mind: the mood strongly suggests alcoholism. Patient is jovial and even facetious, also facile and ingratiating. No objective evidence of loss of memory. Pupils, sluggish to light. Some paralysis and weakness of the legs. Sensation, normal. Knee-jerks absent.

July 8, 1903.—Pupils sluggish. Some incoördination of movements. No Rombergism. Provisional diagnosis of tabes dorsalis.

July 10, 1903.—Temperature suddenly rose to 102° without apparent cause, and as suddenly fell to normal.

July 11, 1903.—Both pupils now react well to light. Pulse feeble and rapid.

July 15, 1903.—Patient suddenly fell in the ward, his legs giving way beneath him.

July 16, 1903.—Temperature again rose to 102°. Blood shows a diminution of the number of red blood corpuscles. Knee-jerks absent. Sensation, normal. Mental state, unaltered.

July 28, 1903.—Improvement in the physical symptoms. Patient feels well except that his legs are weak.

July 30, 1903.—Superficial reflexes all sluggish. Fibrillar twitching of abdominal muscles. Temperature again high.

August 7, 1903.—Patient is now delirious at night. In the daytime merely euphoric and jovial. Physical condition deteriorating; he is emaciating. Fundi normal. Some dulness to percussion at the left apex.

August 8, 1903.—Patient is now delirious also during the day; chatters constantly to himself.

August 10, 1903.—Delirium has disappeared during the daytime. Retention of urine; urine was catheterised. Some muscular rigidity of neck with slight retraction of the head. Occasional strabismus. Very noisy and delirious at night. No convulsions, vomiting, headache or paralysis.

August 11, 1903.—Death. At the autopsy: tuberculous meningitis.

Case 7.—This was an alcoholic case with pronounced generalised arterio-sclerosis. The mental symptoms, which were determined by a cortical hæmorrhage, as the symptoms suggested, might have been the result of the alcoholism or of cerebral arterio-sclerosis, or of both.

T. P., aged 68, commercial traveller. Admitted May 24, 1904.

History.—Patient suddenly lost consciousness and fell in Hyde Park; he remembers nothing from that time until he found himself in the hospital. Admits to very heavy drinking for the past few days. He states that before he fell his right eye and right hand twitched. House surgeon reports that when in the casualty ward the patient had a typical Jacksonian fit ending with some loss of consciousness; the convulsions began in the right forefinger and spread in turn to the other fingers of the

right hand, the right arm, right leg and left leg. His speech has been thick since the attack.

Present state.—May 25, 1904.—Patient a spare, senile-looking man; scanty hair receding from temples; tortuous superficial temporal arteries; cheeks and nose covered with dilated venules; complexion sallow; pulse 72; arterial tension high; radial artery thickened and tortuous. Patient seems vigorous and active and in no distress.

Mental symptoms.—Mood jovial and facetious; garrulous; attention fugitive; memory defective; he confabulates and makes false statements.

Eyes: pupils equal and react normally; no paralysis of external ocular muscles. Speech: thick; dysarthria, no true aphasia. Motor: slight right-sided facial weakness. No paralysis of limbs; grasp strong on both sides. Sensation: no objective alteration; feeling of numbness in right forefinger. Reflexes: knee-jerks much diminished. Heart: enlarged; apex beat thrusting; accentuation of aortic second sound. Lungs: coarse catarrhal sounds. Liver: enlarged.

May 26, 1904.—Still garrulous. Mood euphoric. Confabulates constantly and makes false statements.

May 29, 1904.—Complains of dizziness; had an attack of epistaxis. Discharged.

[The following text is extremely faint and largely illegible. It appears to be a multi-paragraph document, possibly a letter or a report, with several lines of text visible across the page. The content is too light to transcribe accurately.]

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HISTOLOGICAL OBSERVATIONS ON THE
CHANGES IN THE NERVOUS SYSTEM IN
TRYPANOSOME INFECTIONS, ESPECIALLY
SLEEPING SICKNESS AND DOURINE, AND
THEIR RELATION TO SYPHILITIC LESIONS
OF THE NERVOUS SYSTEM.

BY F. W. MOTT, M.D., F.R.S.

INTRODUCTION.

THE relation of Protozoa to the production of widespread diseases affecting men and animals is becoming yearly of greater importance as our knowledge increases. In a certain number of these protozoal diseases *important nervous symptoms are manifested* of direct and indirect importance in regard to mental diseases, which it is my especial business to investigate.

The result has been the development of a new line of research in connection with diseases hitherto mysterious in origin. It had long been known that flagellated organisms played a very important part in diseases of animals. The Tsetse fly disease, which rendered whole tracts of country in Africa uninhabitable to exogenous domestic animals, and the disease of Surra, which destroys enormous numbers of horses and camels in India, and is a matter of supreme importance to the Indian Government, are familiar examples. But it is only within the last few years that a disease, known as sleeping sickness, singularly mysterious and fatal to human beings, has been discovered to be due to a special flagellated organism, a trypanosome, first recognised by Forde and Dutton (1) in a case of Gambia fever and named by them *Trypanosoma gambiense*.

The researches of the Sleeping Sickness Commission of the Royal Society, which was instituted by the foresight and energy of Sir Patrick Manson, led to the discovery by

Castellani (2) of the *T. gambiense* in the cerebro-spinal fluid and blood of a number of cases of sleeping sickness, and laid the foundation stone of the work of Bruce (3), the discoverer of the Tsetse fly disease. He immediately saw the great importance of this discovery, and his work, aided by the other members of the Commission sent out to Uganda to assist him, led to the complete demonstration of the etiology of this disease, namely, that it was due to the *T. gambiense*, which was transmitted from one individual to another by a Tsetse biting fly, the *Glossina palpalis*. Thus it proceeded along the line of travel from the Congo State to Uganda; but it can only occur where the fly exists, and the fly is found especially along the borders of the great lakes wherever there are water and trees. The knowledge of the habitat of the transmitting agent is thus, as in malaria, of supreme importance. The most convincing proof of this is shown by two facts which I will relate: (1) Negroes and even Europeans who have been in a district in which the disease is endemic have left the country and come to Europe, and have afterwards manifested the symptoms of the disease and have died from it several years after leaving Africa; the disease, however, has never spread to other people: (2) Slaves in olden times were taken to America and to the West Indies already infected by the parasite, but not manifesting any signs of the fatal lethargy until they reached America. Then they sickened and died of it, but it was never communicated to other slaves born in the new country (1).

Within the last two years, a discovery of as great importance perhaps as the cause of malaria has been effected by a protozoologist, Schaudinn (4), who showed that a protozoon—the *Treponema pallida*—which he believed was a modified trypanosome, is the cause of syphilis, and Metchnikoff (5) and others have now inoculated anthropoid apes, apes, and other animals, and reproduced the disease. The nearer the animal is to man, the more easily does it take the disease and show similar lesions. The importance of this discovery cannot be over-estimated even by the alienist, for it is generally believed that syphilis is responsible for

a large part of the severe organic nervous diseases and degenerations affecting human beings, including General Paralysis. A fatal disease, the Dum-dum fever (1) or Kala-Azar, characterised by fever and enlarged spleen, has recently been shown to be due to a parasite closely allied to a trypanosoma; this is known as the Leishman-Donovan body, after its discoverers, and the enlargement of the spleen is due to this protozoon finding a suitable habitat in this organ for its development, where it exists in enormous numbers (*vide* figs. 6 and 7, Plate VII.). It may be remarked that the spleen, owing to its anatomical structure, is especially adapted for the multiplication of protozoa which are capable of multiplying in the blood stream, such as the malaria parasite and trypanosomes. The reason is that the junction of the arterial with the venous system is by lacunar spaces; these, no doubt owing to the slowness of the stream through them, would afford a suitable resting place for entrapping the parasites and for allowing their multiplication by fission or conjugation. Recently curious bodies, known as Negri bodies, have been constantly found in variola and rabies, and by some authorities (Calkins) (6) have been regarded as protozoa and the cause of these diseases. Moreover, it is well known that many authorities regard cancer as a parasitic disease of protozoal origin. It is remarkable that nearly all these protozoal diseases, according to Bose (7), are characterised by a general similarity of tissue reaction.

It is the endeavour in this paper to point out the similarity in the tissue reactions of certain chronic trypanosome diseases to those of syphilis. There is indisputable evidence that in chronic infection of *T. Gambiense* and in the infection of horses and animals by *T. equiperdum*, or *Mal de Coit* (*cf.* p. 630), the enlargement of the lymphatic glands is associated with a chronic inflammatory cell hyperplasia similar to the chronic inflammation occurring in syphilis. It has been shown, moreover, that this glandular enlargement is probably due to the presence of the trypanosomes, which act as an irritant there—either by their presence in sufficient numbers, by the production of a toxin

by them, or by their undergoing in the lymphatic glands some undiscovered modification or multiplication. Which-ever it may be, the cell reaction may be looked upon as a defence of the organism against the noxious agent, and in this broad sense, although there may be no phagocytosis, it may nevertheless, be considered an inflammatory reaction, and the condition justifiably termed polyadenitis. The cell hyperplasia which may occur in these protozoal infections is of a similar nature; it is of the fixed tissue elements, endothelial, endothelial plate, conjunctival. In the lymphatic glands, the parasite sets up a hyperplasia in the germ centres where the lymphocytes are produced. It also causes mitosis and active proliferation of the endothelial cells lining the sinuses and of the branched retiform cells, so that a section of the gland in which hyperplasia is occurring exhibits a very striking appearance, which has always been regarded as characteristic of a chronic inflammatory process, namely, proliferated lymphocytes, large mononuclear cells, which may be either plasma cells derived from proliferated endothelial cells or enlarged lymphocytes. The branched retiform cells forming the sustentacular framework exhibit mitosis and proliferation of their nuclei; whether these should be regarded as the nuclei of endothelial plates or as the nuclei of the connective tissue cells is a matter of opinion.

Now what becomes of these cells and why are they formed? To answer these questions it is necessary first to understand why the protozoa get into the glands. In certain trypanosome infections, such as Nagana and Surra, the disease generally runs an acute course and, in animals infected by the parasite, death generally occurs before a chronic polyadenitis exists. But in the infection by *T. gambiense* and *T. equiperdum*, the disease runs a chronic course, and the glands (as in syphilis) are almost invariably affected. There are reasons for believing that in all these diseases the glands nearest the point of primary infection are first infected, and subsequently the glands of the whole body. In Nagana, Jinga (a modified Nagana) and Surra, it is probable that the organisms can multiply in the blood

stream; they can be seen in films undergoing fission, and even in the vessels whorls of trypanosomes from fission can be seen (*vide* fig. 2, Plate VIII.). This, as far as I am aware, has not been figured in any of the film preparations of the blood in sleeping sickness. *T. gambiense*, comparatively speaking, exists only in small numbers in the blood, and generally requires very diligent search to demonstrate its presence, yet it never dies out when once infection has occurred. Where does it multiply? If it cannot multiply in the blood owing to some bio-chemical or bio-physical condition interfering with the process, what medium would it seek?—being a flagellated swimming organism to effect the preservation of the species we should expect some fluid medium. This would be provided in the lymph sinuses of the lymphatic glands and the cerebro-spinal fluid, or in any situation where the blood-vessel is surrounded by a fluid rather than solid tissue. We do not know whether these trypanosomes have the power of boring through the wall of the capillary and thus reaching this fluid medium, or whether by blocking of the capillary a hæmorrhage takes place and the organism escapes into the fluid medium, but certain it is that capillary hæmorrhages are commonly met with in trypanosome diseases; more likely it is that the trypanosome passes through by design and not by accident into a *habitat* found suitable for multiplication. An argument in favour of this view is afforded by the fact that Lingard has shown that the *T. equiperdum* may be found in the vaginal mucus of a mare a fortnight after it has been inoculated by scarification of the labium (*vide* p. 639). Bruce (3) has shown that monkeys in which the blood stream had been infected by *T. gambiense* exhibited the protozoa in the cerebro-spinal fluid subsequently. It would be of interest to see whether other trypanosome infections, such as Nagana and Surra, where immense numbers of trypanosomes can be found in the blood, are followed by infection of the cerebro-spinal fluid.

The cerebro-spinal fluid of men and animals dying of sleeping sickness shows the parasites. Lingard was unable to find trypanosomes in the centrifuged cerebro-spinal fluid

of several fatal cases of dourine, the tissues of which he sent me. The existence of trypanosomes in the cerebro-spinal fluid in all cases of sleeping sickness may be correlated by the profound change in the meninges and perivascular lymphatics of the central nervous system—a change which in all but one important respect is similar to that of cerebro-spinal syphilitic meningitis. That important particular no doubt furnishes the clue to the difference in the symptoms of cerebro-spinal syphilitic meningitis and sleeping sickness. In syphilis the endarterium in all cases is affected as well as the perivascular lymphatics, and the hyperplasia of the endarterium causes occlusion of the vessels and thrombosis, which results in necrobiosis of the neural elements in the area supplied by the vessel. The perivascularitis is similar to that of sleeping sickness, a mononuclear round-celled infiltration, plasma cells, and proliferated glia tissue. The coarse obtrusive symptoms of syphilitic cerebro-spinal meningitis are due to the affection of the endarterium and the cutting off of the blood supply; and the protean character of this disease is related to the manifold combinations of symptoms which may arise from irritative or paralytic phenomena occurring from irritation or destruction of varied and different parts of the central nervous system having different functions.

Universal syphilitic cerebro-spinal meningitis is always associated with an encephalo-myelitis; the most cell infiltration is found at the base of the brain and where the cerebro-spinal fluid is most abundant; the disease is not a late phenomenon of syphilis; the more severe and intractable cases occur in the first few years after infection. Examination of five fatal cases of syphilitic meningitis has shown that the morbid process is universal, and that the hyperplasia is most abundant where the cerebro-spinal fluid is most abundant. May it not be that this is due to the treponema having gained access to the cerebro-spinal fluid just as in sleeping sickness? Hoffmann (8) has recently successfully inoculated an ape with cerebro-spinal fluid of a syphilitic case taken out under all precautions; in another

case the cerebro-spinal fluid injected did not produce any infection; presumably, therefore, the cerebro-spinal fluid in one case contained the organism and in the other did not.

It is now a general belief that general paralysis and tabes dorsalis are of syphilitic origin. According to Fournier (7) they are para-syphilitic degenerative changes due to the effects of the syphilitic poison rather than the result of the specific reaction of the poison. According to Lassar (7), they are very late manifestations of the continuous effect of the attenuated virus. In many respects the tissue changes in general paresis resemble both sleeping sickness and syphilitic meningo-encephalitis. If we consider with Metchnikoff that the treponema has a stimulating effect on the tissues, producing cell hypernutritive activity, and if it be conjectured that those cases of syphilis which are of a mild type (as we know they usually are in general paralysis and tabes) are attended by a prolonged stimulating effect upon the nutrition and activity of the cells of the nervous system, then we may ask ourselves what would be the effect of this prolonged stimulating action, induced possibly by the existence at earlier periods after infection of the treponema in the cerebro-spinal fluid? By analogy with sleeping sickness we might suppose it would set up hypernutritive activity of the conjunctival elements, proliferation of the neuroglia, and proliferation and accumulation of lymphocytes and plasma cells with lymphatic and vascular endothelial proliferation in the meninges and perivascular lymphatics, which we know is the characteristic change of general paralysis, a change which distinguishes it from any other form of mental disease. Neither alcoholic dementia, lead encephalitis, dementia præcox, nor arteriosclerosis show this characteristic vascular and perivascular change. I have seen some cases of general paralysis in which the perivascular cell infiltration might be mistaken for sleeping sickness, so intense and widespread in the brain, especially the sub-cortical structures, was the lymphocyte and plasma cell infiltration and the neuroglia proliferation (*vide* figs. 4 and 5). In these acute cases there is not

much wasting of the convolutions, but the changes in the ganglion cells are much more profound than is usual in the majority of cases of sleeping sickness. One of the two cases of sleeping sickness that were under my care at Charing Cross Hospital, who suffered with epileptiform convulsions for six weeks before death, died from paralysis of the medullary centres; his brain exhibited changes in the cortex which were indistinguishable from those of general paralysis, for besides the meningeal and perivascular cell infiltration, there was increased vascularity and marked distortion and destruction of the columns of Meynert, causing recent degeneration in the pyramidal system, with atrophy and destruction of the tangential and supraradial fibre systems.

The majority of cases of sleeping sickness, however, have no mental disorder, and do not suffer with epileptiform convulsions; the classical symptoms are, an insidious progressive lethargy and paresis, leading to shuffling, unsteady gait, but no paralysis; no signs of pyramidal tract degeneration in the form of clonus or Babinski's sign, although the knee-jerks may be increased. Sooner or later in every case, fine muscular tremors affecting the hands, the face-muscles and the tongue in particular are observed. There is no sensory disturbance; all the special senses and common sensibility are retained, the intelligence and comprehension are unaltered, the only evidence of mental change is slow mental reaction and inability to sustain any mental effort, owing to the difficulty of shaking off the drowsy lethargy for more than a short time. Thus the patient is able only for a brief period to be roused to feel, think, and will in response to stimuli, but during that brief period his feelings, thoughts and actions are comparatively normal. The term "sleeping" sickness hardly expresses the condition. The term lethargy is much more appropriate, and the cause of this lethargy will be discussed later when we have described the pathological lesions.

Towards the end of life in very chronic uncomplicated cases of sleeping sickness signs of irritation and paralysis of the nervous centres may arise; *e.g.*, out of two Europeans

and three negroes that I have personally investigated and who have died in this country, three have run a prolonged course and died from the disease without secondary microbial infection. They were Dr. Mackenzie's (10) case, one of the two cases (9) under my care at Charing Cross Hospital reported by Sir Patrick Manson, and Dr. Bradford's European case. The other negro and European died from secondary microbial infection.

The signs of cerebral irritation may be manifested, as in one of these negroes and in Dr. Bradford's European case, by epileptiform convulsions, and these convulsions may be sufficiently prolonged and pronounced to be associated with marked irritative and destructive changes in the cerebral cortex. Other signs of irritation suggesting meningitis are retraction of the head, stiffness of the neck and flexor contracture of the knees and hips.

The bulbar centres were affected in two of these cases, and paralysis of deglutition, and alterations of the pulse and respiration may be the signs of the neural destruction.

PART I.

THE MICROSCOPIC CHANGES IN THE NERVOUS SYSTEM IN SLEEPING SICKNESS.

I have examined a large amount of material from cases of sleeping sickness, now thirty in all.

(1) Mrs. S., a patient of Sir Patrick Manson who died just under two years after leaving Africa, and who manifested definite signs of sleeping sickness for not more than two months before she died from secondary diplococcal infection. Reported in the *British Medical Journal* (12).

(2) Dr. Bradford's European case, who died just three years after leaving Africa, who must have been infected three years, and who manifested signs of sleeping sickness for over a year.

(3) Three negroes dying in England of chronic sleeping sickness; one prematurely from hyperpyrexia caused by

putrid abscess in the lung. Published in *Pathological Society's Transactions*, 1898 (10) (11).

(4) Material from twenty-five cases (13) dying in Uganda, forwarded to me by the Commissioners. The majority of these suffered with secondary or terminal diplococcal or diplo-streptococcal infection, and this no doubt caused an earlier fatal termination than would otherwise have been the case.

(5) The tissues of nine monkeys inoculated by Colonel Bruce (3) and his assistants by various methods, with blood and cerebro-spinal fluid from sleeping sickness cases.

I have given a full account of the results of the examination of this material in the seventh Report of the Sleeping Sickness Commission, and it is not necessary to repeat the details contained in the appendix of that report.

In every case of lethargy there was the characteristic meningeal and perivascular cell infiltration which I first described and termed a meningo-encephalitis, and there was a parallelism between the intensity and duration of the symptoms and the histological change described. It may therefore be conceded that the perivascularitis is the cause of the symptoms, and according to its progress and intensity so are the progress and intensity of the clinical manifestations of the disease.

Compare, for example, the two European cases.—Mrs. S., who died two years after leaving Africa, and two months after the onset of symptoms, and Dr. Bradford's case who died three years after leaving Africa, and more than a year after the onset of symptoms; the meningeal and perivascular infiltration was very much more marked in the latter. So it was with the negro cases, the longer the symptoms had persisted the more pronounced the histological change. It is probable that many years, Sir Patrick Manson (1) says even as long as seven years, may intervene between the primary infection with *T. gambiense* and death by sleeping sickness. When the signs of lethargy have come on, it is very seldom that the patient lasts more than twelve months.

The histological change observed is one affecting the lymphatic system. A most characteristic feature of the

disease which has been long recognised is the enlargement of the lymphatic glands, especially of the cervical glands. At my suggestion Greig examined the fresh juice of the lymphatic glands and found trypanosomes; he came to the conclusion that there was a polyadenitis and that this was caused by the trypanosomes. There is an increase of the lymphocytes in the blood, but not enough to account for their enormous increase in the perivascular channels of the central nervous system. There are lymphocytes in the cerebro-spinal fluid, and lumbar puncture shows that there is an increase of pressure of this fluid; but Nabarro tells me that when he drew off as much as 50 cc., there was no appreciable change in the lethargy of the patient. This does not, however, prove much, because there may be some internal hydrocephalus. However, as far as my experience goes there is not much flattening of the convolutions, even in very pronounced cases, and there was no optic neuritis observed in any of the cases dying in England, which, if the intracranial pressure had been the principal effective cause in the production, would certainly have been the case. As Dr. Eisath apparently thinks he is the first to suggest intracranial pressure as the cause of the symptoms, I would remind him that I have discussed this fully in the two cases which I recorded in 1898, *Pathological Society's Transactions*. He thinks that proliferation of the neuroglia is the primary and essential cause of the symptoms by interfering with the lymph stream, and that the lymphocytes which are found in such abundance in the perivascular sheaths are thereby intercepted; the symptoms being due to obstruction to the flow of lymph. That there is profound neuroglia proliferation I have long recognised. Whether it is by the irritative influence of the flagellated organism itself, the production of undiscovered modified forms, or the elaboration of a poison, we do not know. Neither Plimmer nor Thomas and Anton Breinl have been able to produce toxic effects by the injection of the blood serum of infected animals filtered through a Chamberland filter into the circulation of healthy animals. As previously pointed out there is abundant evidence to show that the

existence of the trypanosomes in the blood does not apparently damage the vessel walls, except it be by capillary embolism, and such effects as are produced upon the nerve cells when the blood swarms with parasites, is a chromatolysis which could be readily explained by anæmia caused by vascular occlusion associated with the general asthenia from which the animal dies (*vide* figs. 1, 2, 3, 4, Plate VIII.).

Before further considering the changes in the central nervous system of sleeping sickness, let us regard the changes in the lymphatic glands. We shall then be in a position to compare the same with those found in the central nervous system and elsewhere.

The occurrence of irregular remittent pyrexia, in cases of infection by *T. gambiense*, with erythematous urticarial eruptions, suggests association with paroxysmal elaboration of a poison, or the multiplication of the parasite. The great frequency with which the lymphatic glands become enlarged may be associated with the paroxysms of fever and the presence of the protozoa in the glands. It has been shown that this enlargement is not due to microbial infection; it must therefore be due either to the trypanosome or a toxin engendered by it, irritating the gland and causing proliferative hyperplasia of the cell elements. It is a matter of speculation whether the degenerative changes occurring in the neoplastic formation produce cyto-toxins or not; probably by analogy they do not.

HISTOLOGICAL CHANGES IN THE LYMPHATIC GLANDS.

A lymphatic gland in the first stage of swelling shows the following changes. Active proliferation of the lymphocytes in the germ centres so that they are very densely packed together. In the lymph cords and sinuses a very active cell proliferation can also be observed. The oval pale staining nuclei of the endothelial cells lining the lymph channels can be seen greatly increased in numbers and proliferating (*vide* fig. 4, Plate V.). Numbers of large mono-nuclear cells can be seen; these are round, with a deeply-stained round nucleus; they differ from the small mono-nuclears by the more abundant cytoplasm. Others are plasma cells of Marscholkó containing a nucleus with

a wheel-like arrangement of chromatin, and all stages can be traced up to the formation of a typical plasma cell and its final granular degeneration (*vide* figs. 3 and 4, Plate IV.). The origin of these different types of cells has always been a matter of dispute. Moreover, it is a question whether the nuclei seen in the body of the branching retiform cells belong to endothelial plates, or are nuclei of branched connective tissue cells. There is no doubt that these nuclei when subjected to irritation are excited to hypernutritive activity and proliferate (*vide* fig. 5, Plate V.), and produce mono-nuclear cells. There is increased vascularity of the gland, and not infrequently hæmorrhages; in fact, it presents the appearance of chronic inflammation, and we must suppose that the cell proliferation is a defensive reaction to a noxious agent. The cell proliferation goes on until automatically an increase in numbers deprives the cells of sufficient nutrition; or they are destroyed by the virus, and granulo-aqueous degenerative changes occur. These necrobiotic changes may be observed in glands which are sterile by cultural tests for micro-organisms (*vide* fig. 3, Plate IV.). In this and the first stage there is only very occasionally evidence to be found in sections of the existence of trypanosomes. I have rarely in a very large number of sections seen any evidence of trypanosomes or their degenerated remains. Occasionally I have found the dead parasites in the form of attenuated thread-like forms, or macro-nuclei or micro-nuclei (*vide* figs. 1 and 2, Plate V.). According to Greig (3) they can always be discovered in the fresh juice of the enlarged glands (*vide* fig. 3, Plate V.) but Thomas and Anton Breinl (18) consider that they are not more numerous in the glands than in the blood.

In the third stage of very chronic cases, a few of which I have examined (one removed during life and sterile), the products of degeneration had been in great part absorbed and the gland had become dense and fibrous. This is the final sclerous change that occurs in other chronic neoplastic formations, the fibrous conjunctival elements preponderating over the cellular elements. As a rule in sleeping sickness cases death occurs before this can take place.

THE CHARACTERISTIC CELL INFILTRATION OF THE MENINGES AND PERIVASCULAR SPACES OF THE CENTRAL NERVOUS SYSTEM, ITS CAUSE AND ORIGIN.

Is this cell infiltration produced by proliferation of fixed tissue elements, or is the lymphocyte accumulation the result of obstruction and stasis of the lymph stream? To discuss this question it is necessary to make a few remarks concerning the structure of the pia-arachnoid membrane and the perivascular sheath—in fact, the lymph circulation of the central nervous system, including the posterior spinal ganglia and roots. A *résumé*, therefore, of the description given by Cornil et Ranvier (19) will now be given.

THE VESSELS AND PERIVASCULAR CONNECTIVE TISSUE.

The arterioles of the central nervous system are surrounded by a complete sheath (Virchow, Robin, His). This sheath is formed by a delicate structureless membrane, covered on its internal surface by a *discontinuous endothelium*. The cavity thus circumscribed is partitioned by delicate fibrils extending from the internal surface of the sheath to the surface of the vessel and covered at intervals by *discontinuous cell plates*; it also contains a liquid and a certain number of migratory cells. In normal tissues treated by fixative agents, sheath and cavity are easily overlooked, the sheath being closely applied to the vessel. The point where it is always visible is at the bifurcation of the artery, when the sheath appears as a triangle of delicate membrane. The sheath is obvious in many pathological processes. Outside this *lymphatic sheath* of Robin, and connecting it with the remainder of the tissue, there exists a larger more or less thick sheath of loose connective tissue of which the fibrils are orientated parallel to the direction of the vessel; this is the conjunctival perivascular sheath, true emanation of the pia mater, and enclosed on the outside by a condensation of neuroglia tissue, from which however it remains distinct. Note this fact, that the two sheaths, lymphatic and conjunctival, diminish insensibly in thickness in proportion as the vessels decrease in size; so that it is possible that the fine capillaries are in immediate

relation with the neuroglia. The absence of the perivascular lymphatic sheath on these smallest vessels explains why there is little or no cell infiltration around them in sleeping sickness tissues.

The soft membranes.—In the cranium the cavity of the arachnoid is free, its visceral layer is formed by a layer of cell plates supported by a condensation of the pial tissue. In the spinal canal, on the contrary, the cavity of the arachnoid is partitioned by a series of tracts or membranes going from the pia mater to the dura mater. Tracts and membranes are constituted by connective tissue fibrils covered by endothelium. The same as the arachnoid, the encephalic pia mater differs from the spinal pia. On the cerebrum and cerebellum it is formed by a network of fine connective tissue fibres circumscribing large meshes, bundles on the surface of which there exists a *discontinuous investment of connective tissue cells*; in the meshes circulates the cerebrospinal fluid and some sparse migratory cells. Note, however, that on the side of the arachnoid the bundles are condensed in such a manner as to support the arachnoidal endothelium; in their depth they are orientated parallel to the surface of the substance without penetrating into its substance, the adherence between the two tissues being only assured by the vessels which pass directly from the one to the other. Delicate on the surface of the convolutions and of the cerebellar lamellæ, it encloses vessels of different calibre; vessels which ramify in its thickness before penetrating into the nervous substance properly so called; these vessels are surrounded—we have seen it above—by a complete lymphatic sheath which follows them in their ultimate distribution.

The spinal pia mater is much denser, especially in its deeper parts; a tunica adventitia situated immediately outside the lymphatic sheath penetrates with the vessels the substance of the spinal cord.

MORBID CHANGES IN LYMPHATIC STRUCTURES.

The disease is characterised by a chronic polyadenitis (Greig), which is subsequently followed by a chronic inflam-

matory change in the lymphatics of the brain and spinal cord.

All the observers from the earliest time have noticed the enlargement of the lymphatic glands; and Greig, at my suggestion, punctured the glands and examined the fresh juice. He is of opinion, from his observations, that this is an easier and more reliable mode of determining the existence of *T. Gambiense* than examination of the blood or cerebro-spinal fluid. Dutton and Todd (20) came to the same conclusion working in the Congo State. Many natives in Uganda and the Congo State have, however, enlarged glands, and yet are not the subjects of sleeping sickness. They may be, however, and probably in nearly all cases are, candidates for the disease.

Do the trypanosomes get into the glands and *multiply there*, setting up a chronic inflammatory process which terminates in fibrosis? The glands may be inflamed and enlarged, and yet be sterile as regards micro-organisms. It is probable that the trypanosomes infect the lymphatic glands by escaping from ruptured capillaries, or they may become infected by the cerebro-spinal fluid when this secretion contains trypanosomes. Similarly by capillary hæmorrhage the trypanosomes may infect the cerebro-spinal fluid and the lymphatic structures of the central nervous system. If the trypanosomes can set up chronic inflammatory changes in the lymphatic glands (as there is no doubt they do), and microscopic examination of sections reveals but occasional and scanty evidence of their presence, it is quite reasonable to suppose that they can similarly produce chronic inflammatory changes in the lymphatic structures of the central nervous system. We do not know if the trypanosomes produce this chronic irritation by their mere mechanical presence, which seems unlikely, seeing that the vessels may be crammed with trypanosomes in Nagana and Surra without causing lymphangitis. There is, according to Plimmer, Thomas and Anton Breinl (18), however, no experimental evidence that trypanosomes produce a chemical toxin; although that would seem the most probable cause of the chronic inflam-

matory change. The numbers of trypanosomes found in the cerebro-spinal fluid are in no way proportional to the changes found in the central nervous system. Yet there is considerable evidence (*vide* Sleeping Sickness Reports, Royal Society), to show that not until trypanosomes are found in the cerebro-spinal fluid does the chronic inflammatory change take place. If they existed in abundance instead of sparsely, we might consider that this fluid afforded a suitable medium for their propagation, and the absence normally of leucocytes in this fluid might be accounted a cause. On the other hand, the small quantity of proteids which the cerebro-spinal fluid contains would not admit of suitable nutrition.

The posterior spinal ganglia always show some chronic changes, proliferation of the endothelium of the lymphatic capsules of the ganglion cells, together with interstitial lymphocyte accumulation; and these chronic changes may be due to the absorption of toxins from the neighbouring infected paravertebral glands.

In practically all cases of sleeping sickness the cervical glands are enlarged, and the most chronic change is found about the base of the brain. Hence a possibility that the chronic inflammation of the lymphatics spreads along the nerves, spinal ganglia and roots to the central nervous system, and especially along the lymphatics of the nerves and vessels entering the base of the skull. Examination of other tissues, *e.g.*, the heart, pericardium, liver, alimentary canal and testicles, shows, though, generally speaking, in far less degree, an infiltration and accumulation of lymphocytes in the lymphatics, suggesting a defensive reaction.

The meningeal and perivascular cell proliferation and infiltration of the central nervous system, may be regarded as the result of a chronic irritative process connected with the presence of the trypanosomes in the cerebro-spinal fluid.

There is considerable difficulty in distinguishing between nuclei of glia cells and lymphocytes. The chromatin particles of the glia cells, usually two or three, lie in a pale nucleoplasm. The nuclei of the neuroglia cells are, as a

rule, larger than lymphocytes (*vide* fig. 4, Plate II.). They undergo active proliferation not only in the perivascular spaces but in the tissues. The young glia cells lie in pairs, or fours, or more, and may have but little cytoplasm surrounding the nucleus.

Examination of slides of the fresh juice of the glands obtained during life by puncture and stained for trypanosomes, proves conclusively that the cause of the glandular enlargement and of the chronic inflammatory changes met with, is the presence of trypanosomes. Yet the microscopic evidence of the existence of trypanosomes in the sections of the glands is not more satisfactory than the evidence of their existence in the perivascular and meningeal infiltration of the nervous tissue. Chromatin particles which may be micronuclei and macronuclei can be seen as well in one as in the other, and smears of fresh brain sometimes reveal trypanosomes just as the smears of glands.

Smears of glands removed during life from the necks of natives suffering with *T. Gambiense*, but not yet manifesting signs of sleeping sickness, *although sterile as regards micro-organisms*, showed trypanosomes and degenerated products of trypanosomes in the form of small and large chromatin rings (macronuclei and micronuclei). Sections of the same glands exhibited macronuclei and micronuclei and, occasionally, a trypanosome. As the glands were sterile, it may be presumed that the trypanosomes were the cause of the swelling and chronic inflammatory changes. The sections showed increased vascularity and lymphocytes in all stages up to the formation of large plasma cells of Marscholko (as shown in fig. 4, Plate IV.), and large numbers of degenerated swollen plasma cells like those seen occasionally in the perivascular lymph spaces of the brain in sleeping sickness. Moreover, some of the large cells appeared to be endothelial cells which have taken on a phagocytic function and eaten up lymphocytes and chromatin particles. The endothelial cells have proliferated in these inflamed glands, and there is a tendency to fibrosis, nuclear proliferation and thickening of the trabeculae and walls of the lymph sinuses and vessels. Later these glands,

when the inflammation subsides, become fibrous, dense and less vascular. Quite similar appearances were observed in glands removed during life from the neck in cases of pronounced sleeping sickness. These glands were frequently sterile, but the majority which I received that were removed *post mortem*, and quite a number even removed during life, showed points of suppuration in their interior, and an infection with diplostreptococci. I have, however, come to the conclusion that these organisms only play the part of a terminal or late secondary infection due to the breaking down of the defences of the organism. This diplostreptococcal invasion must, however, play an important part in hastening the fatal termination.

In a discussion which took place at the meeting of the British Medical Association at Toronto, August, 1906, when I demonstrated the histological changes in the nervous system of some chronic trypanosome infections, Professor Welch called attention to the fact that Councilman had shown that in every fatal case of small-pox streptococcal invasion occurred. He asked whether the absorption of microbial toxins could be absolutely excluded as a cause of the histological changes? In reply I stated that undoubtedly the fatal termination was hastened in a large number of cases by the microbial invasion, and my observations had shown that a systematic examination of the lymphatic glands had led to the demonstration of organisms where microbial invasion had not been suspected. Yet the etiology of the disease and the study of some of the chronic fatal cases, and particularly the European case under the care of Dr. Bradford, showed that the trypanosomes, apart from microbial invasion, caused the characteristic changes in the nervous system. *In marked chronic cases of sleeping sickness the appearances presented by the lymphatic glands resemble in many ways the infiltration of the perivascular lymphatics of the central nervous system. In the latter there are proliferated lymphocytes, granule cells, plasma cells, proliferating endothelial cells, occasional degenerated trypanosomes and numerous chromatin particles, many of which are probably micronuclei and macronuclei, entangled in the*

markedly proliferated conjunctival sustentacular framework. Figs. 4 and 5, Plate V., show this correspondence of the histological appearance in the lymph sinus of the gland and the perivascular lymphatics of the brain.

We may therefore conclude that the presence of the trypanosomes in these perivascular lymphatics in the sub-arachnoid space (as evidenced by their constant existence in the cerebro-spinal fluid, sometimes in such numbers as to be found without centrifuging) might cause, as in the lymphatic glands, this chronic lymphatic inflammation of the central nervous structures. Infection of the cerebro-spinal fluid may be from the lymphatic glands, or more likely from the blood by capillary hæmorrhages. The European cases and the few animals which have shown the characteristic lesions have all lived over eighteen months after infection; it consequently takes time to effect the change. Lymphatic gland-enlargement is characteristic of all forms of chronic trypanosomiasis of animals.

All cases of sleeping sickness have trypanosomes in the cerebro-spinal fluid at some time or other, and it is probable that the entrance of the trypanosomes into this fluid marks the onset of, and slowly causes, the chronic inflammatory change in the lymphatic system of the central nervous system. The alternative hypothesis is that the trypanosomes, by multiplying in the lymphatic glands, produce a toxin which is absorbed by the lymphatics, and this toxin proceeds along the vessels and nerves to the lymphatics of the cerebro-spinal axis, the probable route being especially from the cervical glands by the lymphatics of the large vessels and nerves entering the base of the skull.

This chronic inflammation of the lymphatics of the brain, with perivascular glia cell proliferation, lymphocyte and plasma cell accumulation, gradually and progressively interferes with the flow of the lymph stream and the circulation of the cerebro-spinal fluid. It is not decided whether the cerebro-spinal fluid functions as the lymph of the brain or whether it simply forms a water jacket around the lymphatic sheath, which is closely applied to the wall of the blood-vessel. The lymphocytes and glia

cells certainly fill up this space and interfere with the normal outflow of the fluid from the cerebro-spinal cavity; consequently when lumbar puncture is performed there is usually evidence of increased pressure; moreover, the fluid contains abundance of lymphocytes. This increased intracranial pressure interferes also with the circulation of the blood in the small vessels, and the characteristic symptoms of the disease, viz., lethargy, tremors and muscular weakness, may be explained by the functional depression of the nerve cells from a deficient nutrition and interference with oxidation processes, brought about by mechanical and bio-chemical interferences with the activities of the nerve cells, and not by neural destruction. This is shown by the patients retaining comprehension of their surroundings and by their intelligent response to questions when roused from their lethargy. A totally different picture to general paralysis (also a meningo-encephalitis) in which there is a profound parenchymatous change, whereas sleeping sickness is a *primary interstitial process*; although later on in the disease, especially when it is chronic and of long standing, marked chromolytic cell changes and a certain amount of destructive degeneration of the neurones do occur.

In all chronic inflammatory conditions of the central nervous system, *e.g.*, tubercular meningitis, general paralysis and syphilitic disease, numbers of lymphocytes are found in the cerebro-spinal fluid. They are also found in sleeping sickness. Where do they come from? They might, if we were assured that they were capable of diapedesis, come from the blood stream, for they are found in greater numbers than normal in the blood. They might come from the blood stream if capillary hæmorrhages occurred, allowing them to escape and proliferate. They might come from the lymphatics or the vessels. Why should they not be formed, however, by a hyperplasia of the nuclei of the endothelial plates themselves? Before considering this question it will be well to offer a few remarks upon the origin and rôle of the lymphocytes.

General remarks and opinions on the origin and rôle of the lymphocytes.—There is a great difference of opinion as to the origin of lymphocytes, as was shown in a discussion on the rôle of the lymphocytes, British Medical Association, Oxford, 1904. Gulland stated that the lymphocytes multiply so easily in connective tissue that the small percentage in the blood is enough for reinforcement.

Ritchie stated, "In a study of inflammatory changes in lymphatic glands I have been able to *trace the separation of the fixed endothelial cells and the assumption by them of phagocytic properties; there is also no doubt that these cells multiply by mitosis in the presence of irritants.* Such changes are especially seen along the lymph paths and sinuses, and appear to me to be of especial interest as we are here dealing with what are merely modified connective tissue cells. It seems that the cells referred to are specialised from the ordinary connective tissue cells, and that fibrotic changes and adhesions do not follow unless the latter become implicated in the reaction process. He considers that non-granular cells with great phagocytic activity may under pathological conditions be derived from fixed cells, *especially from endothelial cells and their homologues.*

Beattie remarked upon the reaction to irritants of the perivascular lymphoid tissue. Maximow maintained that when we have collections of these small round cells they come from the blood-vessels; they are produced rapidly in such enormous numbers that local proliferation is out of the question. Ribbert argues for their local reproduction from pre-existing lymphatic tissue, which is normally present though in a condition but little developed. Beattie agrees with Ribbert, for he says that the increase of lymphocytes in the blood as a result of injection of *B. tuberculosis* is in no way proportional to the local evidence of proliferation in the perivascular lymphoid tissue.

In the Seventh Report of the Sleeping Sickness Commission of the Royal Society (p. 9), I stated as the result of the examination of a large number of sections stained by polychrome and eosin, Mallory and Heidenhain-eosin methods, that the meningeal cell infiltration was the result of an irritative process affecting the pia arachnoid serous membrane, which was manifested not only by a proliferation of the neuroglia cells but also by a proliferation of the endothelial cell nuclei and an infiltration of the pia-arachnoid membrane with lymphocytes, which may become transformed into plasma cells. But sections do not show the

mode of origin of these cells in the same clear and demonstrative manner as the following methods which I have recently adopted. The pia-arachnoid membrane was stripped off small portions of brain from a number of cases of chronic sleeping sickness, including the European case under the care of Dr. Bradford, which was of unusual value, because there was no terminal or secondary microbial infection, and because there was *no noticeable enlargement of the lymphatic glands*. Small portions of the stripped-off membrane were divided by tearing rather than cutting, so that the thin frayed edges could be examined under a high power of the microscope. They were stained by hæmatoxylin and eosin, Leishman's stain, polychrome and cosin, and Eisath's modified Mallory stain, and mounted in Canada balsam. Several interesting facts were observed. *The fibres forming the interlacing network were coarser than natural and much increased*. Many of the vessels were gorged with blood and there were *many capillary hæmorrhages*. A variable number in different cases of large cells containing blood corpuscles or altered blood corpuscles were seen, similar to those seen in sections and shown in fig. 5, Plate III. These cells were usually oval, sometimes round, with the oval or round nucleus pushed up to one end. Sometimes the cytoplasm contains discrete corpuscles, sometimes this *endothelial macrophage* has digested the corpuscles and the cytoplasm has assumed in consequence a uniform orange stain. Some of these cells containing blood pigment had undergone nuclear proliferation, four or five deeply-stained round nuclei could be seen in one cell. The adventitial sheath of the arteries can be distinctly seen, and there is often evidence of endothelial cell proliferation shown by an increase in number of large pale oval nuclei, many of which can be seen undergoing mitosis and proliferation; they resemble the endothelial nuclei seen in the lymph sinus of the lymphatic glands (*vide* fig. 4, Plate V.). But the great mass of cell infiltration is in the meshwork of the pial trabeculæ of the sub-arachnoid space and its prolongation as a sleeve around the vessels entering the grey matter.

Preparations stained by logwood and eosin and Van Gieson's fluid exhibit two kinds of nuclei, viz., (1) large, pale, oval, less often roundish nuclei with a delicate nuclear membrane and very fine intranuclear network similar in all respects to the oval nuclei of a lymph sinus; (2) smaller round or irregular-shaped more deeply-stained nuclei with a narrow investing cytoplasm, also large cells containing similar deeply stained nuclei, and not infrequently some cells, two or more, even as many as six, round nuclei, which are sometimes unequal in size and always uniformly, diffusely and deeply-stained throughout. These cells are endothelial cells undergoing endogenous nuclear proliferation. Moreover, I have observed the same curious forms of nuclear division figured on p. 645.

The endothelial cells of the lymphatic sheath of Robin, and the endothelial plates lying upon the trabeculae of the subarachnoid space and the pial sleeve of the vessels, as the result of the chronic irritation produced by the presence of the trypanosomes in the cerebro-spinal fluid, undergo a progressive formative hyperplasia similar to that of the lymphatic glands.

Dr. Eisath claims that his method does not stain the nucleus of the lymphocytes. I have therefore figured a preparation of stripped pial tissue stained by his method, which shows that both the small and large mononuclear cells may be produced by active proliferative hyperplasia of endothelial cells.

I have observed in these preparations large flat endothelial cells without any processes exhibiting the following appearances of hyperplasia: (a) With the cytoplasm stained pink and with an oval or round nucleus in the centre stained light yellow. (b) The same form of cell can be seen undergoing endogenous nuclear proliferation. (c) The same form of cell dividing or divided into small mono-nuclears in which there is only a relatively small surrounding pink-stained cytoplasm. Besides, we find cells (d) which morphologically resemble the branched retiform cells of connective tissue of the lymphatic gland with a large oval unstained nucleus. These nuclei appear

to undergo division to form hyaline mono-nuclear cells like the similar cells which are seen proliferating in the inflamed lymphatic glands (*vide* fig. 3, Plate V.). The increase of the large and small mono-nuclear lymphocytes in the blood may be due to this cell hyperplasia in lymphatic structures. The meningeal and perivascular infiltration (*vide* fig. 1, Plate I.), is due not only to active endothelial cell proliferation *in situ*, but also to accumulation of the lymphocytes by conjunctival

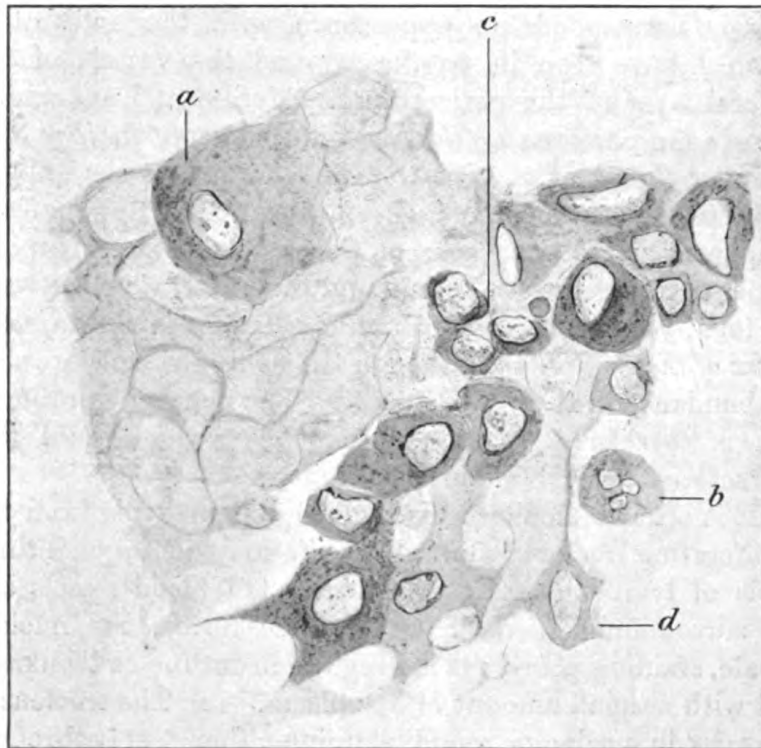


FIG. 1.—Small portion of pial tissue stained by Eisath's method mounted on the flat. Magnification 500.

proliferation and consequent obstruction to the outflow of the lymph along the vessels, also obstruction to the escape of the cerebro-spinal fluid from the cranio-spinal cavity. The infiltration is found especially around the vessels having a lymphatic and pial sheath; this sheath disappears on the smallest vessels, therefore we can easily understand why it is that the smallest vessels and capillaries show little or no

investing sheath of cell infiltration; however, in chronic cases lymphocytes and especially plasma cells can be seen closely applied to them (*vide* figs. 2 and 3, Plate I., fig. 2, Plate II.). Do the branching processes of the *neuroglia cells* form a meshwork around the larger vessels and cause obstruction, or is the meshwork in which the mononuclear cells lie merely the thickened and proliferated trabeculae of the connective tissue cells of the lymphatic and pial sheath? The infiltration around the large vessels and in the membranes entirely corresponds in appearance with the infiltration which I have seen in patches around the vessels of the visceral layer of the pericardium. Moreover, I am *unable to trace the processes of the neuroglia cells any farther than the outer sheath of the infiltration*. Again, no place shows the perivascular and meningeal infiltration better than the lymphatic and pial sheaths of the vessels in the soft membranes covering the cerebellum and their extensions between the folia, *yet there are no neuroglia cells seen in the adjacent cortex of the cerebellum*, although the neuroglia cells are seen in abundance in the white matter. The neuroglia proliferation is *therefore not essential* for the production of this characteristic perivascular cell infiltration.

It is often difficult to distinguish lymphocytes from the proliferating nuclei of glia cells. We may distinguish three kinds of lymphocytes in the transected blood-vessels and the surrounding tissues: (1) Hyaline forms, the nucleus is pale, staining poorly; it is irregular in outline or lobulated, and with a small amount of cytoplasm. (2) The nucleus is irregular in outline or round, staining either deeply throughout, or the chromatin is arranged in the form of a wheel with a central nucleolus from which straight spokes pass out to a nuclear membrane ending in little knobs; there is hardly any surrounding cytoplasm. (3) Large mononuclears possessing phagocytic functions, the main difference from the smaller variety being the much larger amount of surrounding cytoplasm; they form the so-called plasma cells and are developed from the proliferating endothelial plates, the same as the smaller lymphocytes; the latter can grow into them. Whether an endothelial plate will form small

or large mono-nuclear cells apparently depends largely upon the number of nuclei the original nucleus divides into (*vide* fig. 1.)

In sections of vessels cut obliquely so that the outermost structure of the wall is shown—that is the part in contact with the sleeve of cerebro-spinal fluid—I have seen endothelial cells lying like the scales on the bark of a fir tree, or a tessellated pavement, and sometimes presenting all the appearances of the typical plasma cells of Marscholko. It appears to me a mere quibble whether plasma cells are developed from lymphocytes or endothelial cells, since in my opinion there is sufficient evidence to show that both plasma cells and lymphocytes in chronic inflammatory conditions develop from endothelial cells of serous membranes and perivascular lymph structures, and from endothelial plates of connective tissue.

THE NEUROGLIA.

It is often a matter of some difficulty to distinguish young neuroglia cells from hyaline lymphocytes. By the use of the modified Heidenhain stain employed by my late assistant, Dr. Watson, and the polychrome and eosin stain, I was able to see all the changes which he described in juvenile general paralysis, and just as in that disease neuroglia cell overgrowth is a leading histological characteristic, so it is of sleeping sickness and chronic trypanosome infections. The young neuroglia cells may be recognised by their pale-staining round or oval nuclei, with a delicate intranuclear network containing one or two small nucleoli and a definite nuclear membrane. The chromatin substance is stained blue; surrounding the nucleus is a well-defined zone of protoplasm stained pink of irregular quadrate or polygonal outline (*vide* fig. 4, Plate II.). These cells can be seen in groups and undergoing active division, especially in the neighbourhood of the ganglion cells. The various phases in the development of the neuroglia cells, as so admirably described and figured by Dr. Watson, can be seen, viz.: (1) The nucleus surrounded with an indefinite amount of cytoplasm, polygonal or irregularly quadrilateral in shape; (2) the protoplasm tending to form short spike-

like processes, sometimes giving it a star-like appearance; (3) increase of cytoplasm around nucleus and commencing formation and differentiation of the *darkly-stained* Weigert stiff fibrils; (4) further development of the Weigert fibrils and extension of one on to the wall of a vessel, there ending in a foot-like expansion; (5) further increase of development of the Weigert fibrils and differentiation from the pink-stained protoplasm on which they appear to lie; (6) the protoplasm is almost entirely differentiated into fibrils, and the nucleus is shrunken and stains deeply like the fibrils, so that the whole glia cell is stained a deep blue-black.

Distribution of the glia proliferation.—The distribution varies in different cases; it is almost entirely a primary interstitial overgrowth and not secondary to neural degeneration. It exists in a marked degree in cases which during life presented no symptoms pointing to destruction of nervous elements. In some very chronic cases in which there have been many epileptiform seizures, there may have occurred sufficient degeneration in the pyramidal tracts to give rise to a secondary system sclerosis, but this is exceptional.

The glia proliferation which is not visible to the naked eye in sections of the spinal cord becomes very manifest when examined with a low power, and there is a diffuse glia proliferation, as I first pointed out in the two cases which I first investigated. This diffuse sub-pial glia proliferation affects the periphery of the cord and spreads inwards along the septa; it is not only met with in the white matter but is evident also in the grey matter. The situations in the brain where glia proliferation is most obvious in general paralysis, are the situations in which it is most obvious in sleeping sickness. Thus it is well advanced in the most superficial layers of the cortex, where large branching cells with deeply-stained Weigert fibrils can be seen forming a sub-pial feltwork. The large branching cells with Weigert processes extending on to the small vessel walls, cannot be seen so well amidst the columns of cells as in the subjacent white matter. From the examina-

tion of the brains of two monkeys that died from sleeping sickness after experimental inoculation, the glia-cell overgrowth and extension of processes on to the vessels appeared to be more marked than the perivascular mono-nuclear infiltration (*vide* figs. 1 and 2, Plate III.), as if this tissue was the first to respond to the irritation of the noxious agent. However, examination of a case, Mrs. S., in whom symptoms only existed for two months, did not show a glia proliferation in excess of the mono-nuclear infiltration, nor could I find any neuroglia proliferation in Bara Risgallah, a chronic case of infection by *T. gambiense*, who died of pneumonia and pneumococcic meningitis after an illness of ten days, but who prior to this illness had displayed no symptoms of nervous affection.

CHANGES IN THE CENTRAL CANAL OF THE SPINAL CORD.

Not only is there evidence of a chronic irritative action of the cerebro-spinal fluid by the cell proliferation in the meningeal and perivascular lymphatics, but in all chronic cases the central canal of the spinal cord is filled up owing to a proliferation of the cells of the ependyma. I found this had occurred in quite juvenile subjects. It was so in the little Congo negro boy, who died in Charing Cross Hospital in 1898, and I was of opinion then that this fact afforded evidence of a very chronic nervous affection caused by some irritating agent (*vide* fig. 2). It was the same with the juvenile cases from Uganda—Sempagana, aged 8, Hamesi, aged 12, and Kaperi, aged 8-10. Such change denotes, then, a chronic process of considerable duration. It is probable in the light of our present knowledge of the possible long duration of the disease that these subjects were infected when quite infants.

Examined under a high power, the nuclei of the cells lining the spinal canal may often be seen undergoing active proliferation, and specimens stained with polychrome and Heidenhain eosin method exhibit large pale nuclei with a thin membrane and chromatin granules stained blue surrounded by a pink cytoplasm, often with numerous processes. In some very chronic cases the glia proliferation

has led to the formation of abundant Weigert fibrils. In the grey matter around the central canal numerous glia cells having a similar appearance can be seen.

For further information concerning neuroglia changes, I will refer the reader to the careful observations of Dr. Eisath, but I desire to say that I deem it of little importance whether the glia proliferation precedes the mono-nuclear cell infiltration, or whether by its doing so it obstructs the flow of the lymph and entangles the mono-nuclear cells.



FIG. 2.—Central canal of 1st cervical segment of spinal cord, showing proliferation of ependymal cells to form glia cells. As the proliferation proceeds from within outwards, the ring of new young cells increases, leaving a more fibrillary substance behind in the centre, which fills up the canal. Around the ring of cells there is also a zone of more fibrillary substance. The fibrils are the processes of the glia cells. Magnification 90.

Nor do I regard it as of much importance whether we speak of this formative cell hyperplasia as a chronic inflammatory process or not. *The important fact to recognise is that this meningeal and perivascular infiltration is a hyperplastic reaction of fixed tissue elements to a noxious agent, the *T. gambiense*; so far we are on certain ground; it is, however, a matter of speculation whether this tissue reaction is due to: (a) the relatively few trypanosomes which can be demonstrated in the fluid; (b) the elaboration of a toxin by them; (c) a transition to some hitherto undiscovered modified forms.*

CHANGES IN THE SMALL VESSELS AND CAPILLARIES.

The capillaries in the pia and in the brain tissue show the following changes, but these are not nearly so marked as in general paralysis of the insane.

The nuclei of the endothelial cells may undergo proliferation, and in the neighbourhood of the capillaries and small vessels there are often numerous lymphocytes, plasma cells and glia cells, sending a process on to the wall of the vessel; but I fail to find evidence of sprouting new capillaries as seen in general paralysis, nor can I but very rarely find any evidence of the Stäbchenzellen or rod cells described by Alzheimer, and regarded by him as very characteristic of this disease. These Stäbchenzellen, I consider, are probably collapsed capillaries (*vide* fig. 6, Plate II.).

The marked proliferation of the vascular endothelium with hyaline degenerative changes of the small vessels so frequently met with in general paralysis, is hardly ever seen in even the most chronic case of sleeping sickness, nor can I find any evidence of endarteritis so generally met with in all cases of syphilitic brain disease.

Capillary hæmorrhages are met with in all forms of trypanosome disease, and probably are the result of obstruction by the organisms.

CHANGES IN THE NEURAL ELEMENTS.

Although the meninges are in many cases obviously thickened and the convolutions flattened (indication of some intracranial pressure), yet there is no naked-eye wasting of the brain. The depth of the grey matter of the cerebral cortex is not appreciably diminished, although the vessels both in the grey and white matter may appear somewhat congested. In very chronic cases, after the brain has been hardened in formol-Müller solution, then washed in water, the transections of the vessels may appear like dark dots surrounded with a pearly-grey ring. The dark centre is due to the blood contained in the vessel, and the surrounding zone of a pearly-grey colour is due to the perivascular cell infiltration.

I have not observed granulation of the ependyma of the ventricles, so characteristic of the meningo-encephalitis of general paralysis of the insane. Moreover, the wasting of the grey matter of the cerebral cortex, so characteristic of this disease, is not met with in sleeping sickness. The convolutions are broad and of normal size, and the sulci tend to be obliterated in sleeping sickness; whereas in general paralysis the convolutions are shrunken from atrophy of the neural elements, cells and fibres, and the sulci are consequently broad and deep. In both diseases there is obvious meningeal thickening, and septal and perivascular changes, but here it seems to me the similarity ends. But this statement becomes more apparent and convincing when the microscopic changes are described. Moreover, a comparison of the size of the remaining structures of the central nervous system show that in general paralysis there is a primary neuronc atrophy which does not occur in sleeping sickness. Thus to the naked eye the spinal cord in the latter disease may appear normal as regards amount of grey and white matter, whereas in general paralysis the cord is often much reduced in size, and there is very obvious neuronc atrophy.

The naked-eye appearances therefore point especially to a primary parenchymatous degeneration in general paralysis with chronic interstitial and meningeal inflammation, whereas in sleeping sickness the morbid change is primarily interstitial and with some secondary parenchymatous atrophy.

MICROSCOPIC EXAMINATION OF THE NERVE CELLS AND FIBRES.

Cells.—Stained by the various modifications of Nissl method, sections of the various structures of the central nervous system, viz., cortex cerebri, cerebellum, pons, medulla oblongata and medulla spinalis, also spinal ganglia, exhibited certain changes, but in comparison to the interstitial perivascular and meningeal change they were inconsiderable, thus contrasting markedly with general paralysis.

Let us consider, firstly, the cortex cerebri. Under a low power, the five layers of Meynert can usually be easily differentiated. The most obvious change is in the subpial molecular layer of Cajal, but the three layers of pyramids above the layer of granules are generally distinctly seen, the cells usually retaining their pyramidal form, their apical processes being straight as a rule, and the cells arranged in columns, a picture quite different to that seen in general paralysis.

The abnormal feature, apart from the perivascular infiltration, is the abundance of nuclei of neuroglial cells and lymphocytes scattered about and often lying in groups in the perineuronal spaces.

The great majority of the specimens of nervous tissues from sleeping sickness cases which I have examined, have shown marked changes in the ganglion cells of the central nervous system when examined under a high power. I have reason to believe that these changes are largely due to the effects of secondary or terminal microbial infection, to pyrexia, or in some cases, hyperpyrexia. But a terminal or secondary microbial invasion with toxæmia and fever would produce universal effects, and in such cases one finds that throughout the nervous system the ganglion cells present a chromolytic change, the whole ganglion cells staining with polychrome and eosin a diffuse purple, and showing an absence of the Nissl pattern of the cytoplasm. In the first case I examined in 1898, the patient died of septic hyperpyrexia from an abscess in the lung. Although the interstitial meningeal and perivascular change was most pronounced, the neuronie degeneration was comparatively slight, although the patient was in the third stage of the disease. The outline and shape of the ganglion cells of the central nervous system did not present marked changes, but every cell showed a diffuse chromolytic change. This was obviously due to the high fever. Nevertheless, in chronic cases marked chromolytic changes and atrophy of dendrons do occur in the ganglion cells, especially in those regions where the perivascular infiltration is most severe, and where, in consequence, a certain amount of blood stasis

takes place. I have observed this in the medulla oblongata ; and the affection of the important cardiac and respiratory centres in this region may, in a few uncomplicated cases, be the ultimate cause of death. The changes in the ganglion cells may therefore be considered as due (1) to the primary lymphangitis, and (2) to secondary microbial toxæmia. It is difficult to differentiate the cells which are affected by the one cause from the other.

I consider, however, that the chronic change is indicated in those cells in which (1) there are appearances of atrophy of the dendrons, the protoplasmic processes being either attenuated or broken off ; (2) there is a perinuclear chromatolysis, the cytoplasm still exhibiting some remnants of a pattern of Nissl granules in the circumference of the cell and on the dendrons ; (3) the nucleus is large and clear and often eccentric. Sometimes a dead ganglion cell may be seen being devoured by phagocytes (*vide* figs., Plate VI.). The cells of the spinal cord usually show much less change than the cells of the medulla oblongata and cerebral cortex. The cells of the posterior spinal ganglion usually show chromatolysis but not destruction (*vide* fig. 1, Plate VII.).

The appearance of the cells in acutely fatal trypanosome infections, *e.g.*, Surra and Jinga in animals, could be accounted for by the anæmia caused by the blood change and the obstruction of the small vessels by the trypanosomes. In the brain of the rabbit dying of Surra, the ganglion cells all showed a shrinking of the cytoplasm, a marked chromatolysis and disappearance of the Nissl granules, and swelling of the nucleus, and a change not unlike that observed in some forms of experimental anæmia (*vide* fig. 3, Plate VIII.).

EXAMINATION OF THE CENTRAL NERVOUS SYSTEM FOR FIBRES BY WEIGERT AND MARCHI METHODS.

In cases uncomplicated by terminal microbial infection there is a certain amount of fibre atrophy proportional to the cell atrophy described. This atrophy is most obvious in the tangential layer of the cortex cerebri, where the fibres in places are greatly diminished, or even absent.

There may also be some diminution of the fibres in the super-radial and inter-radial systems, especially in chronic cases. There is, however, in the brain as in the spinal cord, no definite system-tract sclerosis, the result of atrophy of a neuronic system. Generally in the lateral columns corresponding to the pyramidal systems some degenerated fibres can be seen by Marchi method, but the glia proliferation tends to follow the distribution of the septa rather than to accord with any definite atrophy of a system of nerve fibres.

By Marchi method, the cerebrum, cerebellum, spinal cord and spinal ganglia were examined in a number of cases. In most instances the results were unsatisfactory owing to a generally diffuse blackening of the myelin sheaths and the deposition of black granules. I consider this change was probably the result of acute changes in the myelin, brought about by terminal microbial toxæmia, fever, &c. Some few of the cases, however, did not show this generalised change in the myelin, and a certain number of fibres showing Wallerian degeneration were found. These changes we may regard as definite and indicative of neuronic decay.

SECONDARY OR TERMINAL MICROBIAL INVASION.

After death, in the great majority of the cases which I have examined, secondary or terminal microbial infection had occurred.

Sometimes the diplococci were found in sections of the blood-vessels as well as in the membranes, indicating a generalised infection (*vide* fig. 2, Plate V., and fig. 6, Plate IV.).

The culture experiments of Novy (30) and McNeal show that infection of the culture media by micro-organisms interferes with the growth of the trypanosomes. The cases in which I found trypanosomes in the blood contained in sections of vessels of the nervous system, were two chronic cases uncomplicated, as far as I know, by microbial infection. In the European case, under the care of Sir Patrick Manson, the histological investigation of which Low and I reported, the trypanosomes disappeared from the blood a short time

before death ; this was coincident with a generalised diplo-streptococcal invasion. The chronic case, under the care of Dr. Bradford, showed no microbial infection ; but in a large proportion of the cases the fatal termination is accelerated by secondary microbial invasion.

When there was an invasion of the central nervous system by diplococci, it seemed probable that this occurred by way of the lymphatics proceeding from infected paravertebral glands. Sections of the cervical nerves, spinal ganglia and posterior roots, in some cases enabled me to trace the course of the microbial infection along the lymphatics of these structures (*vide* fig. 1, Plate IV.).

EXAMINATION OF NERVOUS TISSUES OF ANIMALS EXPERIMENTALLY INFECTED BY TRYPANOSOMES.

Experimental Evidence.—Animals inoculated with *T. Gambiense* usually die before the characteristic lesions of the nervous system can occur. I have examined the tissues of nine animals (monkeys) which were inoculated at Entebbe in one way or another with *T. Gambiense*. They were all said to have exhibited the characteristic lethargy, but it is very difficult to differentiate (according to my experience) between a monkey that sits moping when profoundly ill, and an animal which exhibits a lethargy on account of the brain lesion.

The tissues of the brains of all the animals sent to me, with the exception of two, showed no characteristic change. The vessels of the brain were empty and there was no meningeal or perivascular infiltration. Several of these animals had survived the infection (as proved by the existence of trypanosomes in the blood) one year. One was subsequently infected with diplo-streptococci from a sleeping sickness case ; yet there was no sign of the meningo-encephalitis met with in every case of human sleeping sickness. This was the experience apparently of Ayres Kopke.

(1) The tissues of one monkey inoculated with *T. Gambiense* showed, however, the characteristic lesion of

human sleeping sickness. This case was reported by Major Leishman and Captain Harvey (24). It survived the infection eighteen months. I have examined portions of the tissues kindly given to me by Major Leishman, and find that there is a very marked neuroglia proliferation of the perivascular lymphatics, endothelial cell proliferation and lymphocyte accumulation, and a few plasma cells around the vessels of the brain in all the situations examined. In fact, the lesion in no respect differs essentially from that of human sleeping sickness (*vide* fig. 2, Plate III.). The cerebro-spinal fluid and tissues in this case were, according to Leishman, sterile.

(2) A monkey, upon which large numbers of infected flies were allowed to feed on several successive occasions, exhibited trypanosomes in the blood and cerebro-spinal fluid, and died eight months after the first fly feeding, having presented symptoms of lethargy. Reports of the Sleeping Sickness Commission of the Royal Society, No. VI., pp. 107 and 108.

The subcortical white matter of this animal showed a considerable glia cell proliferation in relation to the vessels (*vide* fig. 1, Plate III.), but there was little evidence of lymphocyte accumulation. The spinal cord also showed a glia proliferation. It is possible, therefore, that the glia cell proliferation precedes the lymphocyte accumulation in the perivascular spaces.

(3) Monkey 99. The medulla oblongata and tissues about the base of the brain showed a commencing subpial, septal and perivascular glia proliferation.

Examination of the nervous tissues of animals inoculated with Nagana, Surra and Jinga trypanosomes, and which died within a few months of infection, the blood, swarming with trypanosomes, or modified or degenerated trypanosomes, showed no perivascular or meningeal changes.

(1) The brain of a rabbit inoculated with Surra, which died three months later, was kindly given me by Dr. Plimmer, and showed the following appearances in sections. By any of the staining methods employed nearly all the blood-vessels showed masses of trypanosomes, as

the coloured drawings exhibit (*vide* figs. 2, 3, and 4, Plate VIII.). Single trypanosomes could be seen in the capillaries; in the larger vessels solitary trypanosomes and whorls of trypanosomes and plasmodial masses, which are either degenerated trypanosomes consisting of a zoogloal mass in which many deeply-stained macro-nuclei and micro-nuclei can be seen, or of amoeboid forms, described by Plimmer and Bradford (26). But in spite of this extraordinary trypanosome infection the blood-vessels showed little or no inflammatory reaction. The perivascular lymph spaces showed no lymphocytes, and the ganglion cells showed only marked chromolytic changes; otherwise there was nothing noteworthy in the nervous system.

(2) The brains of two oxen infected with Jinga trypanosomes were examined. The animals died within three months of infection; the results of the examinations were extremely interesting and will be given in some detail.

Experiment 162 (loc. cit., p. 171).—The cortex cerebri, the cerebellum, medulla and spinal cord were examined, and all yielded the same results. With a magnification of 1,200 diameters, the capillaries and vessels were found to contain chromatin bodies closely resembling Leishman bodies, except that they were smaller, measuring from 1 to 2 μ , much more frequently 1 μ , rarely as large as 2 μ . They were either circular or oval rings, or had the appearance of the chromatin particles situated at the two poles. Several drawings from photomicrographs are given to illustrate their appearance and their numbers. Some of the capillaries show immense numbers, and in some transections of larger vessels these bodies may be observed lying in a zoogloal mass (*vide* figs. 3, 4, and 5, Plate VII.).

Individual bodies exhibit some diversity in their forms, indicating division. A large number of stained particles (which may be micro-nuclei) can be seen.

The Jinga trypanosome, as the accompanying drawing shows (*vide* fig. 2, Plate VII.), is comparatively a large organism, as seen in the blood of a monkey which was inoculated with it. Its oval macro-nucleus is much larger than these chromatin bodies which are seen in the vessels.

If these chromatin bodies, as Leishman would affirm, are the macro-nuclei of trypanosomes, then it is difficult to explain why a dozen or more of the chromatin bodies can sometimes be seen lying in a space which could be covered by one trypanosome. Still, the trypanosomes may have degenerated elsewhere and the macro-nuclei have been carried into the capillaries. In view, however, of the researches of Captain Rogers (24*a*) regarding Leishman bodies being altered phases of trypanosomes, and the contention of Plimmer and Bradford *re* the existence of amœboid forms of trypanosomes, it is possible that these chromatin bodies may be some phases in the life of the trypanosomes in the blood. For comparison a drawing is given of the appearances presented by Leishman bodies in the spleen and splenic blood from preparations kindly lent by Sir Patrick Manson. The preparations were made from a fatal case of Kala-Azar.

Experiment 202, Ox (loc. cit., p. 174).—This animal died within three months of infection. Portions of the brain were stained in bulk by polychrome and eosin, and sections cut 5 μ thickness after embedding in paraffin.

In this way the contents of the vessels were but little disturbed, so that trypanosomes existing in the serous fluid contained in the blood-vessels were recognisable in great numbers. The appearances of the trypanosomes and their modified forms are seen in fig. 1, Plate VIII.

It may be mentioned that in these two cases there was no sign of meningo-encephalitis, and there was no diplo-streptococcal infection. The ganglion cells showed chromolytic changes, and there were *many minute capillary hæmorrhages*, probably due to plugging of the capillaries by the organisms. I have frequently observed in the lymphatic glands, meninges and perivascular lymphatics of the brain of sleeping sickness, chromatin rings, very similar to, only smaller than, the chromatin rings seen in the vessels of Jinga- and Surra-infected animals, of the trypanosomic origin of which there can be no shadow of doubt. It is therefore probable that a number of the chromatin particles seen in the tissues of sleeping sickness are all not

débris of degenerated cells but *débris* of degenerated trypanosomes or their modifications. Especially would this argument be valid if the tissue, as in the case of the glands removed during life, had been shown to be sterile. Moreover, I have seen appearances in sections of lymphatic glands removed during life, of thread-like attenuated forms of trypanosomes resulting from division, not unlike those figured by Gray and Tulloch (25) as multiplying by fission in the stomach of the *G. palpalis* (*vide* figs. 1 and 2, Plate V.).

It is probable that animals infected directly by blood from sleeping sickness cases containing *T. Gambiense* might, if they were inoculated in the abdomen or hind legs, show changes in the spinal cord before they showed changes in the brain. This may account for the fact that Plimmer's (27) rats only showed changes in the spinal cord; and in dourine or *mal de coit* the changes in the central nervous system are primarily and most markedly severe in the lumbo-sacral region of the spinal cord, especially of the posterior and lateral columns.

Further experiments on animals should, in my opinion, be carried out, anthropoid apes being used, and the neck should be chosen as the seat of inoculation.

COMPARISON OF THE LESIONS OF SLEEPING SICKNESS WITH THOSE OF SYPHILITIC BRAIN DISEASE AND GENERAL PARALYSIS.

In sleeping sickness there is a slow progressive extension of inflammatory reaction to irritation, manifested by lymphatic endothelial and conjunctival tissue proliferation, leading to a perivascular and meningeal infiltration with lymphocytes and plasma cells. The *endothelium of the blood-vessels* is scarcely at all affected, so that although there is a tendency to stasis and a progressive anæmia of the nervous substance, it is seldom so complete as to lead to a coarse and obvious local necrosis as in syphilis, or a local or generalised necrobiosis as in general paralysis. In sleeping sickness the neurons suffer from *functional depression* as a result of interference with their gaseous and

nutritive exchanges. This interference is caused by circulatory disturbances in the flow of blood and lymph, and it is brought about by the lymphangitis and the increase of intracranial pressure. This functional depression of the neurons may be correlated with the perinuclear chromatolysis; the breaking off of the dendrons may indicate chronic degenerative processes, but the fact that there is little evidence of system gliosis or Marchi degeneration shows that most of the changes are functional rather than necrobiotic. Moreover there is no obvious wasting of the central nervous system as in general paralysis.

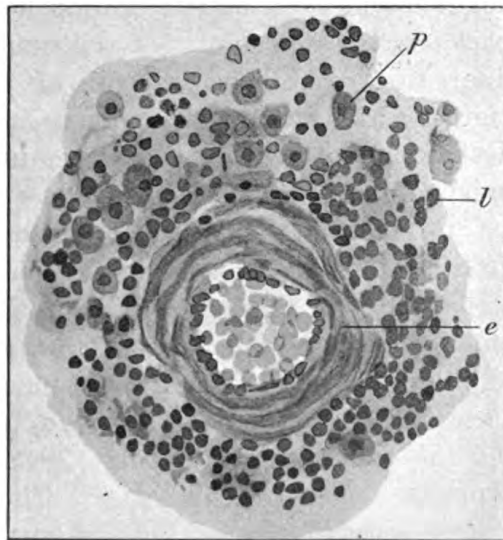


FIG. 3.—Section of syphiloma of the brain showing vessel (*e*) with thickened endarterium, (*l*) lymphocytes, (*p*) plasma cells. Magnification 300.

In multiple gummata or generalised syphilitic brain disease in which there is stupor, the symptoms may be partly due to intracranial pressure and transitory circulatory disturbances, but sooner or later vascular occlusions occur and terminate in areas of necrosis. If we examine a syphiloma before caseation has taken place we find that it resembles other syphilitic lesions in earlier stages, viz., a formative hyperplasia of fixed tissue elements, *endothelial and conjunctival*. The accompanying fig. 3 is a section of

syphiloma, and we observe the same perivascularitis as in sleeping sickness, but there is also a marked endovascularitis; the endothelial proliferation is not far enough advanced to have occluded the vessel nor has thrombosis occurred, consequently necrotic changes have not yet taken place. The destruction of the neural elements in syphilitic brain disease depends upon occlusion of the larger arteries by thrombosis following endarteritis; the lesions like the clinical symptoms are random, coarse and obtrusive.

General paralysis is a slow, insidious, progressive disease in which there is not only an *interstitial perivascular and meningeal infiltration* and neuroglia proliferation like that of sleeping sickness, but there is in addition a *marked progressive parenchymatous necrobiosis* of the neurons. I am of opinion that this necrobiosis is both of primary and secondary origin. Cases in which there are unilateral fits leading to destruction of cerebral substance in the corresponding hemisphere, show acute changes in the cells obviously due to vascular causes. In general paralysis there are proliferative and degenerative changes in the walls of the capillaries and small vessels.

As Alzheimer (28) in his admirable work has shown, there is hyalin swelling and proliferation of the endothelial cells of the capillaries, sprouting, and the tendency to form new capillaries, and the existence of numbers of rod cells which are in my opinion collapsed capillaries. These vascular changes are not observed in sleeping sickness, so whether they are the essential cause or the results of the neuronal decay or degeneration it is difficult to say. The histological changes in general paralysis resemble those of sleeping sickness in the conjunctival and lymphatic endothelial hyperplasia with formative proliferation of neuroglia, lymphocytes and plasma cells. In acute cases the infiltration may be widespread and so abundant as to resemble sleeping sickness; the accompanying fig. 4 shows a subcortical vessel with perivascular infiltration. Examination of the cortex of this case, however, exhibits marked distortion of the columns of Meynert, with destructive necrobiosis of the neurons. The neuroglia proliferation, as before remarked,

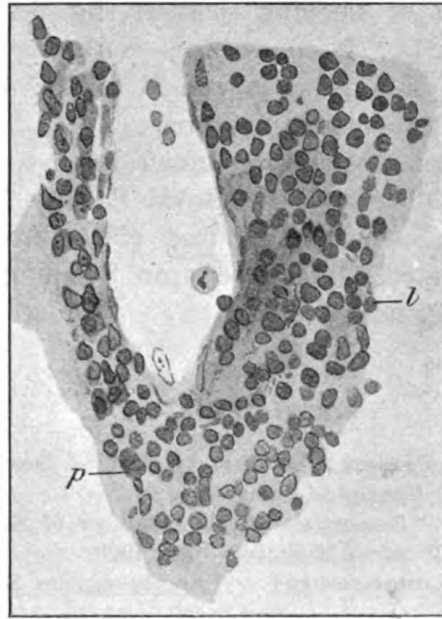


FIG. 4.—Section of small subcortical vessel, acute general paresis, (*l*) lymphocytes, (*p*) plasma cells. Compare with fig. 3, Plate II. Magnification 300.

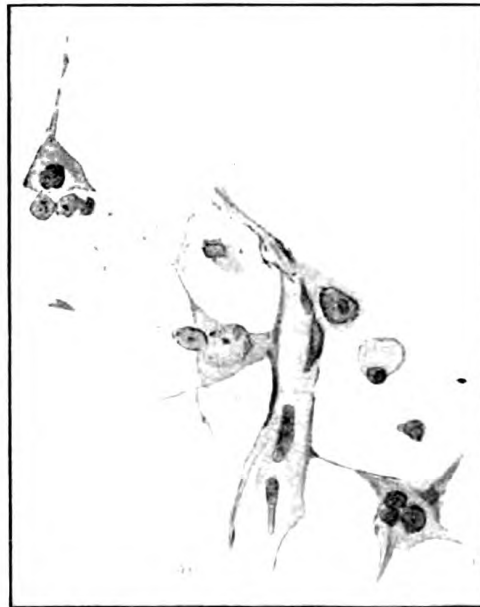


FIG. 5.—Small vessel, acute general paresis, showing neuroglia cells with proliferating nuclei and processes extending on to the small vessel. As in sleeping sickness there is little or no infiltration around because there is no pial or lymphatic sheath. Magnification 400.

resembles that of sleeping sickness, fig. 5. The constant and most important feature of this disease is the progressive dementia, and this is proportional to the abiotrophy and destruction of the cortical neurons.

In conclusion, I wish to acknowledge my indebtedness to the Colonial Office and the Royal Society for kindly permitting me to use the coloured plates from my Report No. 7, Histological Observations on Sleeping Sickness and other Trypanosome Infections.

BIBLIOGRAPHY.

- (1) MANSON, Sir PATRICK. Lectures on Tropical Diseases. Lane Lectures, 1905. Constable, London.
- (2) CASTELLANI. "Researches on the Etiology of Sleeping Sickness," *Journal of Tropical Medicine*, June, 1903.
- (3) BRUCE and COMMISSIONERS. "Reports of the Sleeping Sickness Commission."
- Vol. I. (1) CASTELLANI. "Presence of Trypanosomes in Sleeping Sickness."
- (2) BRUCE and NABARRO. "Progress Report on Sleeping Sickness in Uganda."
- Vol. II. (3) CHRISTY. "The Distribution of Sleeping Sickness."
- (4) CASTELLANI. "Adult Forms and Developmental Forms of the Trypanosomes found in Sleeping Sickness."
- (5) LOW and CASTELLANI. "Report on Sleeping Sickness from its Clinical Aspects."
- Vol. III. (6) CHRISTY. "The Epidemiology and Etiology of Sleeping Sickness in Equatorial East Africa."
- (7) THEOBALD. "Report on a Collection of Mosquitoes and other Flies from Equatorial East Africa."
- Vol. IV. (8) BRUCE, NABARRO and GREIG. "Further Report on Sleeping Sickness in Uganda."
- Vol. V. (9) AUSTEN. "A Provisional List of Diptera."
- (10) NABARRO and GREIG. "Further Observations on the Trypanosomiases (Human and Animal) in Uganda."
- Vol. VI. (11) GREIG and GRAY. "Continuation Report on Sleeping Sickness in Uganda."
- (12) GREIG. "Report on Sleeping Sickness in the Nile Valley."
- (13) AUSTEN. "The Distribution of Tsetse-flies."
- (14) GRAY and TULLOCH. "The Multiplication of the Trypanosoma in the Alimentary Canal of the Glossina Palpalis."
- (4) SCHAUDINN. *Münchener Med. Wochenschrift*, May, 1905, p. 1,028.
- (5) METCHNIKOFF et ROUX. *Annales de l'Institut Pasteur*, 1904-05-06.

- (6) CALKINS, Professor GARY N. "Pathogenic Protozoa," *Popular Science Monthly*, November, 1906.
- (7) BOSE. "Les Maladies Bryocytiques (Maladies à Protozoaires)." *Centralblatt für Bakteriologie* (Band original), 1906.
- (8) HOFFMANN. "Mittheilungen und Demonstrationen über experimentelle Syphilis, Spirochæten pallida, &c." *Centralblatt für Bakteriologie*, Band xxxviii., Original, p. 99.
- (9) MOTT. "The Changes in the Central Nervous System of Two Cases of Negro Lethargy, sequel to Dr. Manson's Clinical Report," *Brit. Med. Journal*, vol. vi., p. 1,666, 1899.
- (10) MOTT. "A Case of Negro Lethargy, by Stephen Mackenzie, with a Note on the histological Changes of the Nervous System by F. W. Mott," *Trans. Path. Soc., Lond.*, vol. li., part ii., 1900.
- (11) MANSON and MOTT. "African Lethargy, or the Sleeping Sickness," *Trans. Path. Soc., Lond.*, vol. li., part ii., 1900.
- (12) MOTT and LOW. "The Examination of the Tissues of a Case of Sleeping Sickness in a European," *Brit. Med. Journal*, April, 1904.
- (13) MOTT. "The Cerebro-spinal Fluid in Relation to Diseases of the Nervous System," *Brit. Med. Journal*, December, 1904.
- (14) BETTENCOURT, KOPKE, GOMEZ DE REZENDE, CORREA MENDE, "La Maladie du Sommeil," Lisbon, 1903.
- (15) WARRINGTON. "A Note on the Condition of the Central Nervous System in a Case of African Lethargy," *Brit. Med. Journal*, vol. ii., p. 929, 1902.
- (16) SICARD et MONTIER. "Recherche Bact. et Histol. dans un cas de Maladie du Sommeil chez un blanc," *La Presse Med.*, December, 1905.
- (17) MOTT. Histological Observations, &c. Report VII. of the Sleeping Sickness Commission.
- (18) THOMAS and ANTON BREINL. "Trypanosomes, Trypanosomiasis and Sleeping Sickness. Report, vol. vi., part ii., 1905." Thompson Yates and Johnston Laboratories, University of Liverpool.
- (19) CORNIL et RANVIER. *Manuel d'Histologie Pathologique*, vol. ii.
- (20) DUTTON and TODD. Gland Puncture in Trypanosomiasis. Thompson Yates and Johnston Laboratories' Report, vol. vi., part ii., 1905.
- (22) WATSON. "The Pathology and Morbid Histology of Juvenile General Paralysis." *Archives of Neurology*, vol. ii.
- (23) KOPKE. "Investigações sobre a Doença do Somno," *Archivos de Hygiene e Pathologia Exoticas*, vol. i., fasc. 1.
- (24) HARVEY. "Report on a Case of Experimental Sleeping Sickness in a Monkey," *Journal Royal Army Medical Corps*, May, 1905.
- (24a) ROGERS. "Preliminary Note on the Development of Trypanosoma in Cultures of the Leishman Donovan Bodies of Cachexial Fever and Kala Azar," *Lancet*, July 23, 1904.
- (25) MARSHALL. The present state of knowledge is well summed up by Marshall (F. W. M.). "Trypanosomiasis or Sleeping Sickness," *Review of Neurology and Psychiatry*, February, 1906.
- (26) BRADFORD and PLIMMER. "The Trypanosoma Brucei, the Organism found in Nagana or Tsetse-fly Disease," *Quart. Journal Micro. Science*, vol. xlv., April 20, 1905.

- (27) PLIMMER. "Note on the Effect produced on Rats by the Trypanosomata of Sleeping Sickness," *Proceedings of the Royal Society*, vol. lxxiv., No. 504, February 24, 1905, pp. 388-390.
- (28) ALZHEIMER. "Histologische Studien zur Differenzialdiagnose der Progressiven Paralyse."
- (29) MOTT. "Observations on the Brains of Men and Animals Infected with Various Forms of Trypanosomes," *Proceedings of the Royal Society*, vol. B. 76, 1905.
- (30) NOVY. *Journal of Infectious Diseases*, vol. ii., No. 2, March, 1905.

DESCRIPTION OF PLATES.

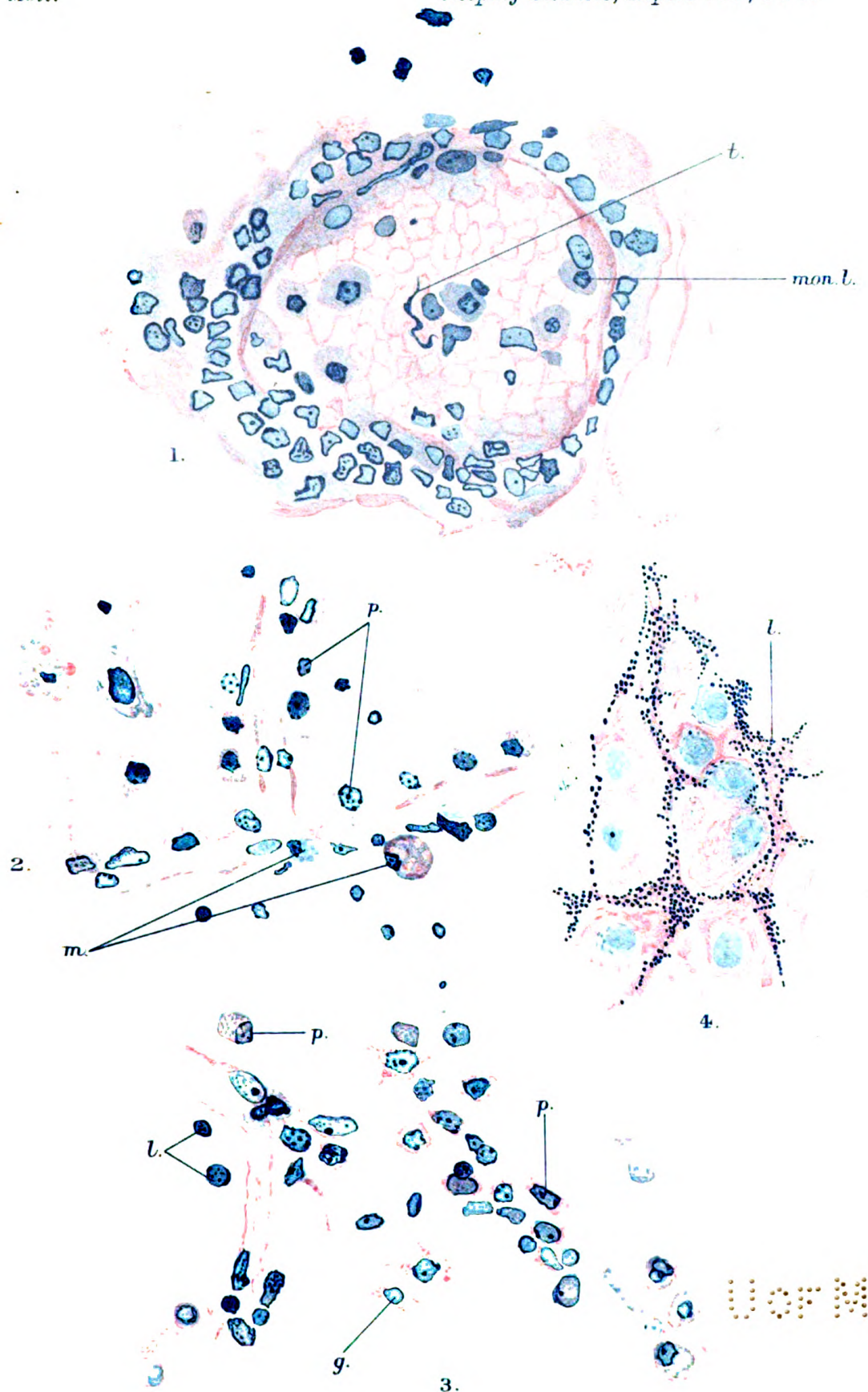
Except where otherwise stated all sections were stained with methylene blue and eosin.

PLATE I.

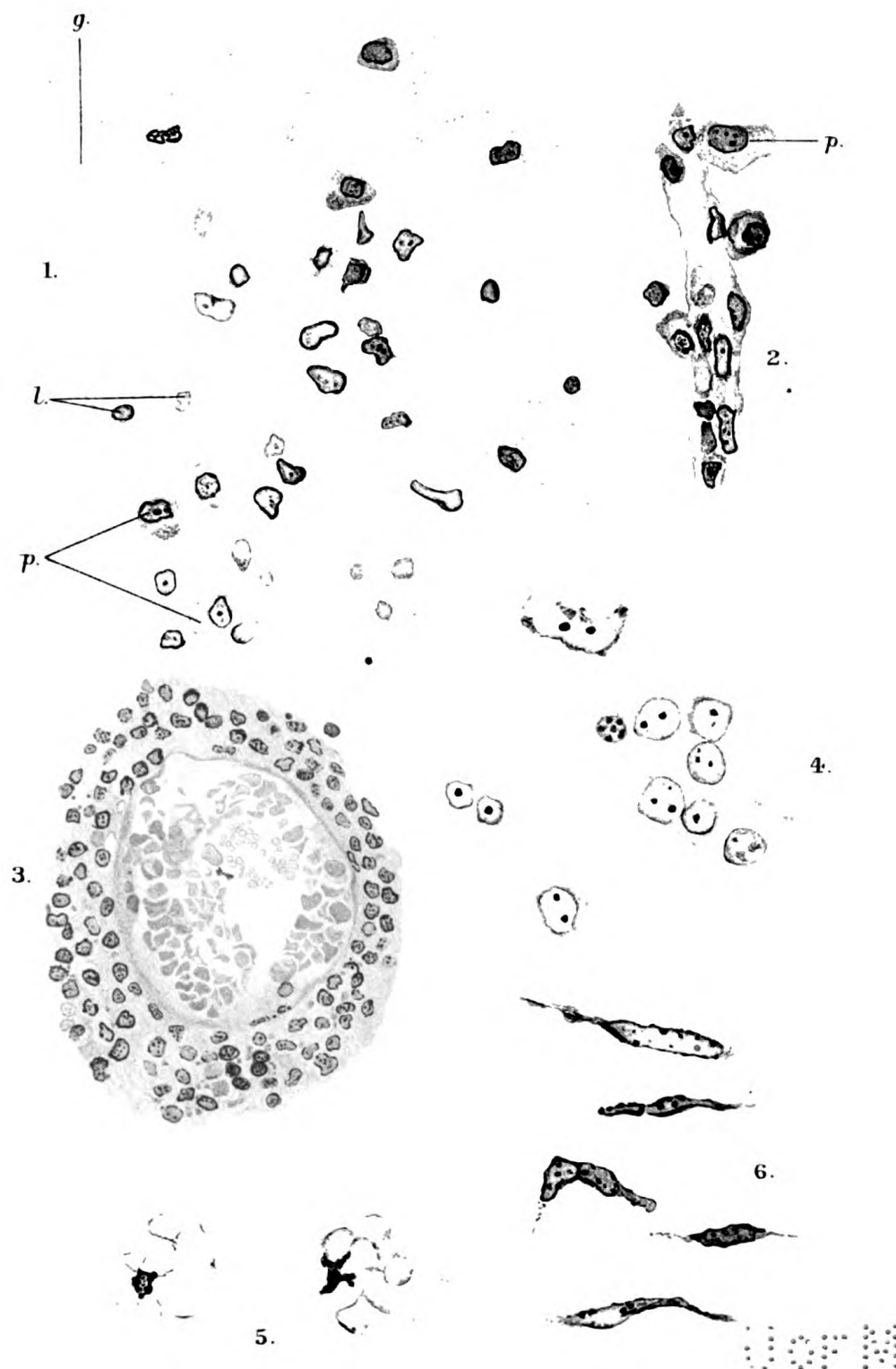
- FIGS. 1-4.—Appearances presented by the vessels of the brain in a very chronic case of sleeping sickness.
- FIG. 1.—Transection of small vessel of medulla oblongata, showing perivascular infiltration with hyaline lymphocytes. In the centre of the blood vessel is a trypanosome (*t*). Amidst the blood corpuscles there are numerous small and large mono-nuclear leucocytes (*mon. l.*). Magnification 500.
- FIG. 2.—Small vessel, with plasma cells (*p*) and large granule cells, which I have termed morular cells (*m*). They correspond to Körnchen Zellen of Alzheimer. Magnification 500.
- FIG. 3.—Small vessel dividing into two capillaries, showing nuclear proliferation of the endothelial cells; in the neighbourhood are plasma cells (*p*), lymphocytes (*l*), and glia cells (*g*). Magnification 500.
- FIG. 4.—Section of spinal ganglion, showing lymphocyte interstitial infiltration (*l*). Magnification 120. Same section is shown more highly magnified in fig. 1, Plate VII.

PLATE II.

- FIG. 1.—Three large glia cells (*g*), their branches ending in a network around and upon a small vessel; lymphocytes (*l*) and plasma cells (*p*) are seen scattered about. Magnification 500.
- FIG. 2.—Small vessel, showing endothelial nuclei proliferated, and three plasma cells. Magnification 500.
- FIG. 3.—A transection of a vessel in a very chronic case of sleeping sickness, showing marked perivascular infiltration. Magnification 250.



1000



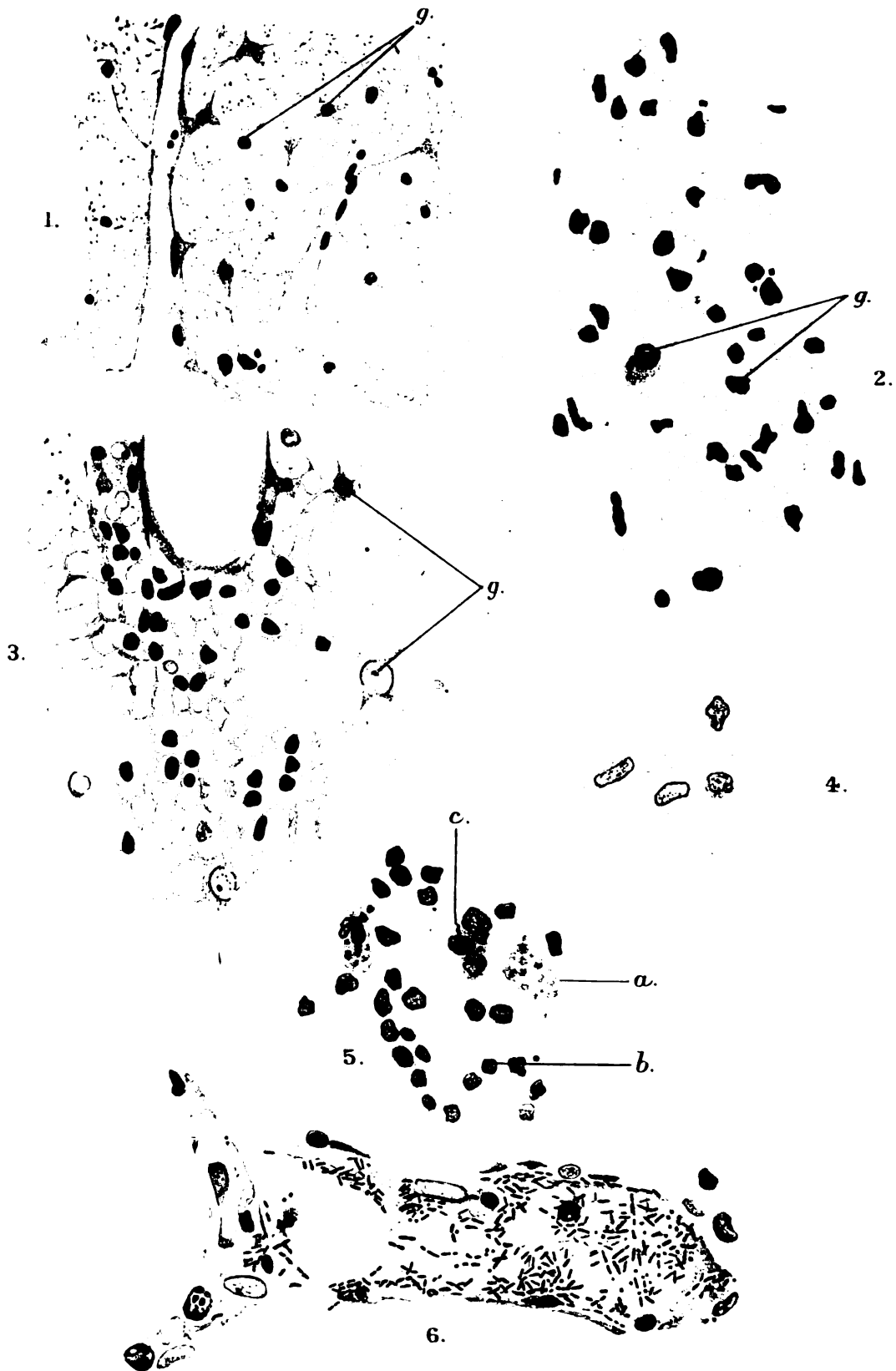


FIG. 4.—Active proliferating young glia cells found in great numbers in sleeping sickness tissues. The pale nucleus, with distinct nuclear membrane, contains chromatin granules, with an arrangement indicating mitosis. Surrounding the nucleus is the pink-stained cytoplasm, with a tendency to form star-like processes. Magnification 500.

FIG. 5.—Two large morular cells from a very chronic case of sleeping sickness. Magnification 500.

FIG. 6.—Rod cells (Stäbchen Zellen) are rarely met with, although occasionally appearances like fig. 6 are seen. Magnification 500.

PLATE III.

FIG. 1.—Section of subcortical matter of brain of monkey that died after infection by trypanosomes caused by infected flies being allowed in considerable numbers to bite the animal. Experiment 228. There is little or no perivascular lymphocyte infiltration, but a considerable increase in size and number of the perivascular glia cells. Magnification 490. Stained by Heidenhain method.

FIG. 2.—Section of subcortical white matter of monkey that died eighteen months after infection and showed the characteristic lesion of sleeping sickness. Harvey and Leishman. The glia proliferation is well seen, and in the meshwork of the branching fibres which form the reticulum of the perivascular lymphatic space (which is seen in longitudinal section) are numerous lymphocytes. The body and reticulum of the glia cells are stained pink in the section; the lymphocytes and neuroglial nuclei are stained blue. Magnification 600.

FIG. 3.—Transection of a blood-vessel in the sub-cortical white matter—sleeping sickness. The lymphocytes are pale and unstained. Magnification 480. Eisath's stain.

FIG. 4.—Small vessel of brain of monkey in which the blood-vessels of the brain had been rendered empty and collapsed by ligation of all four arteries. This is to show the perivascular space filled with cerebro-spinal fluid, and the supporting neuroglial trabeculæ, such as are shown in the drawing, are only seen at intervals. It can be understood that if these trabeculæ are greatly increased the lymphocytes will tend to be caught in the meshes. Magnification 500.

FIG. 5.—Shows macrophages (a) containing blood corpuscles, the result of a hæmorrhage into the cerebro-spinal cavity; lymphocytes (b) and diplococci (c) which are undergoing lysis. In the immediate neighbourhood could be seen crowds of diplococci and diplo-streptococci, which stained deep blue. Magnification 500.

FIG. 6.—Vessel of the brain with bacilli, the result of secondary infection. Magnification 500.

PLATE IV.

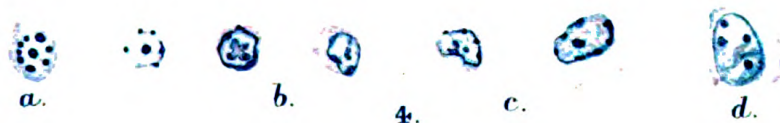
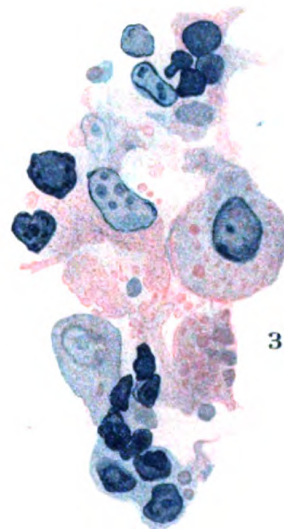
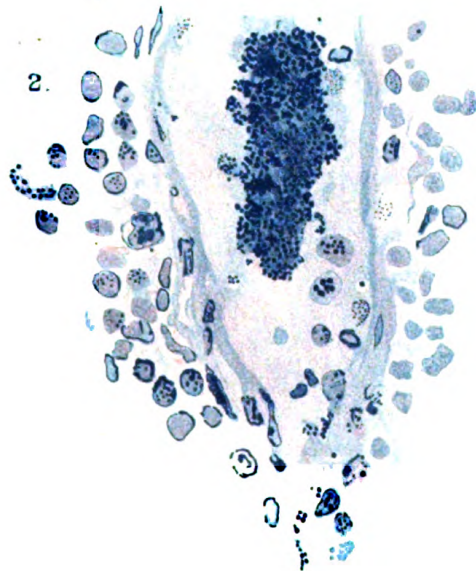
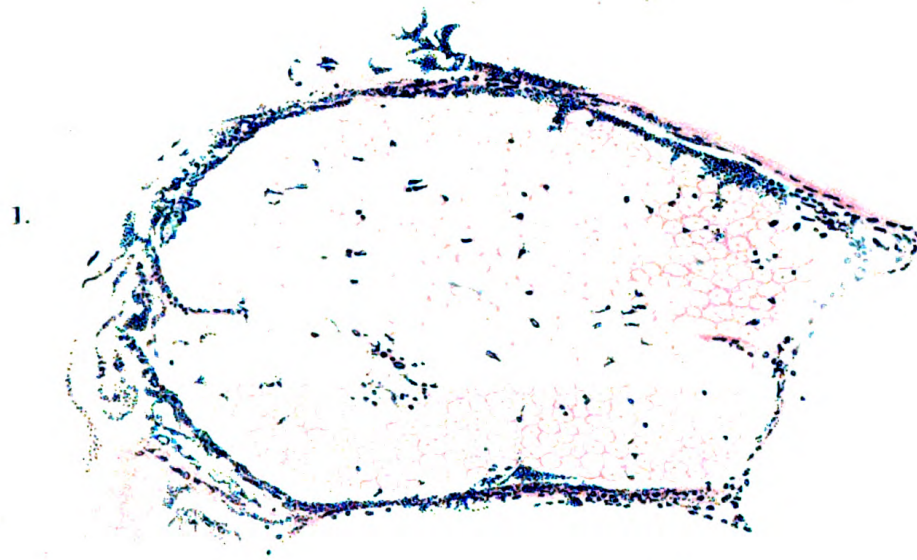
- FIG. 1.—Transection of cervical nerve close to the spina ganglion, showing an infection of the sheath of the nerve by diplo-streptococci. The adjacent lymphatic glands showed points of suppuration. Magnification 200. (a) The micro-organisms, magnified 500. Case 69, L.L.
- FIG. 2.—Vessel of the internal capsule of a case of acute sleeping sickness, with a large plug of cocci. Magnification 500. Stained by Gram's method.
- FIG. 3.—Various degenerated cells seen in section of sterile lymphatic gland. Magnification 1,000. Leishman stain.
- FIG. 4.—Lymphocytes and their transition to plasma cells *a*, *c*; *d*, degenerated plasma cell seen in section of lymphatic gland. Magnification 1,000. Leishman stain.

PLATE V.

- FIG. 1.—Thread-like bodies and granules deeply stained, seen in section of lymphatic gland, probably altered and degenerated trypanosomes. Magnification 1,000.
- FIG. 2.—Trypanosome in a lymphatic gland section amidst disintegrated cell products. Figs. 3 and 4 (Plate IV.), and figs. 1 and 2 (Plate V.), are drawings made from the same sections, 5 μ in thickness, stained with Leishman's stain and prepared from an enlarged cervical gland removed during life from a case (Bara Risgallah) of trypanosome fever, before symptoms of sleeping sickness had occurred. Magnification 1,000.
- FIG. 3.—*Trypanosoma Gambiense* in smear of fresh gland juice, several lymphocytes, micronuclei. Magnification 1,000.
- FIG. 4.—Section of lymphatic gland from a recently fatal case of sleeping sickness in a European. The glands in this case were not much enlarged. There is a very marked proliferation of the endothelial nuclei. Magnification 500.
- FIG. 5.—Proliferation of the connective tissue cells of the reticulum of a lymph sinus; marked proliferation of the nuclei of the endothelial cells seen. This chronic change closely accords with the change observed in the perivascular lymph spaces of the central nervous system. Magnification 500.
- FIG. 6.—Various granules and products of cell (and trypanosome?) degeneration seen in the perivascular infiltration of the central nervous system in sleeping sickness. Magnification 1,000.

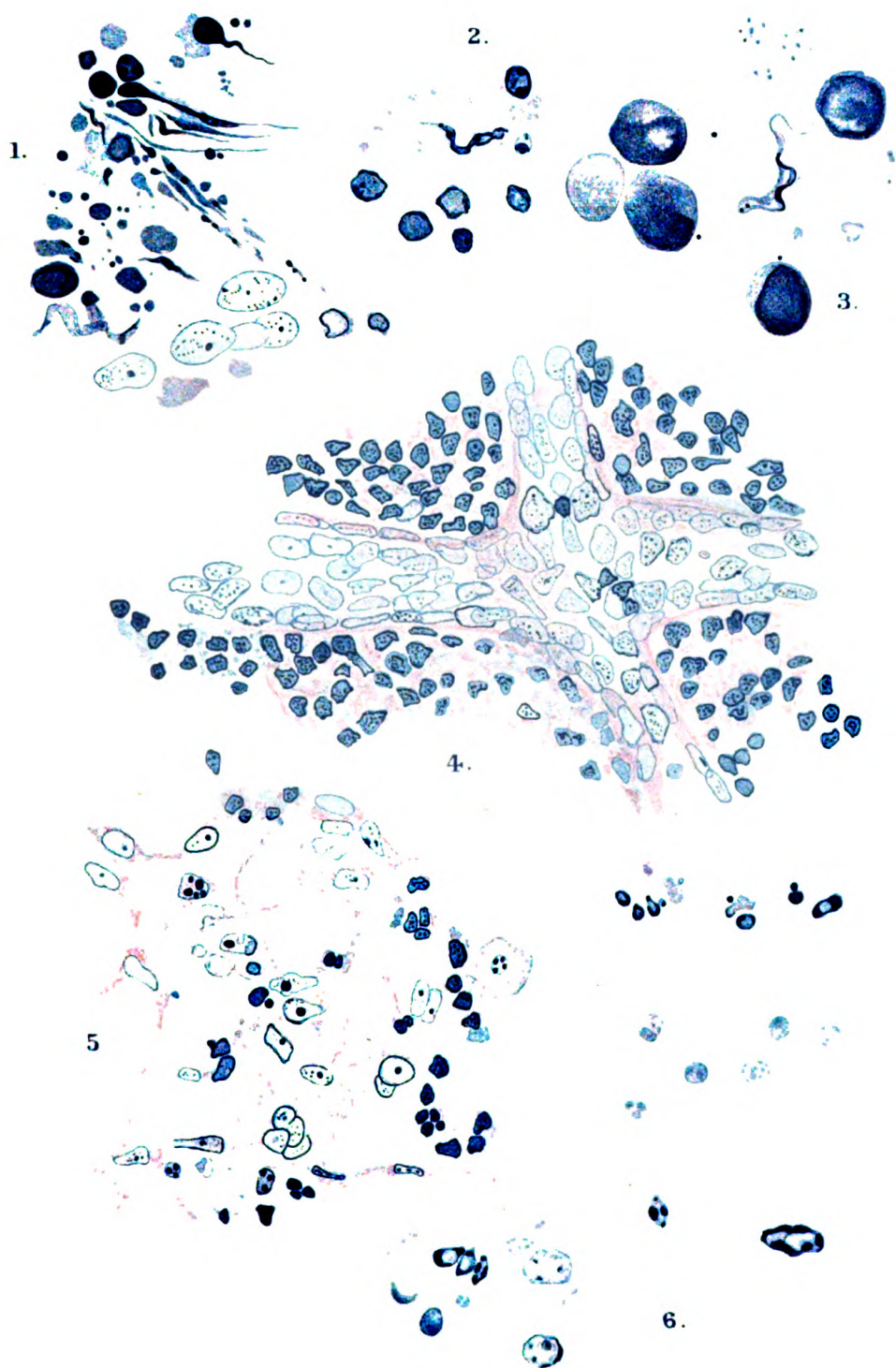
PLATE VI.

- Appearance of various pyramidal cells of the cerebral cortex in cases of very chronic sleeping sickness, showing various stages of chromatolysis and chronic degeneration. One cell is covered with phagocytes (*h*). Magnification 500.



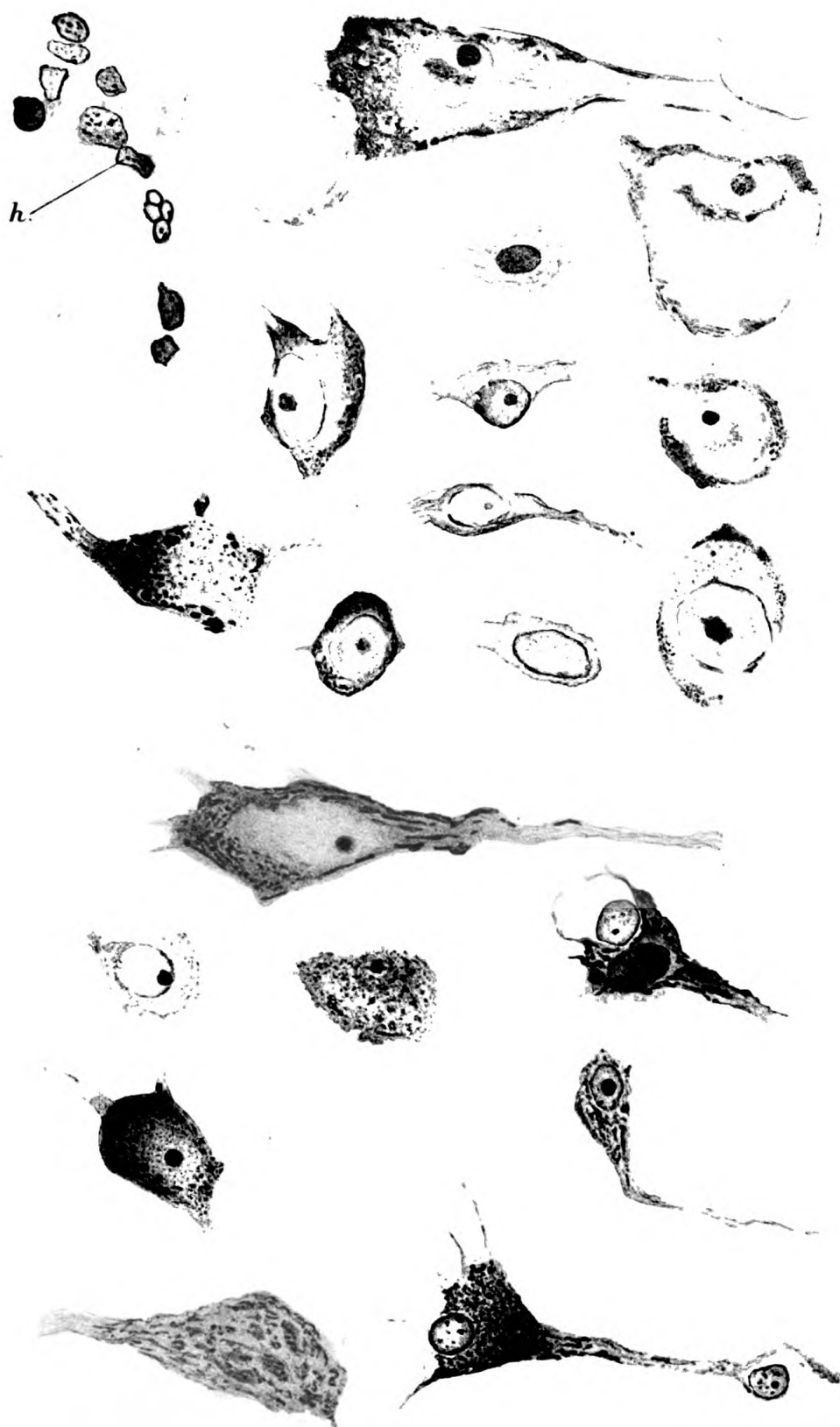
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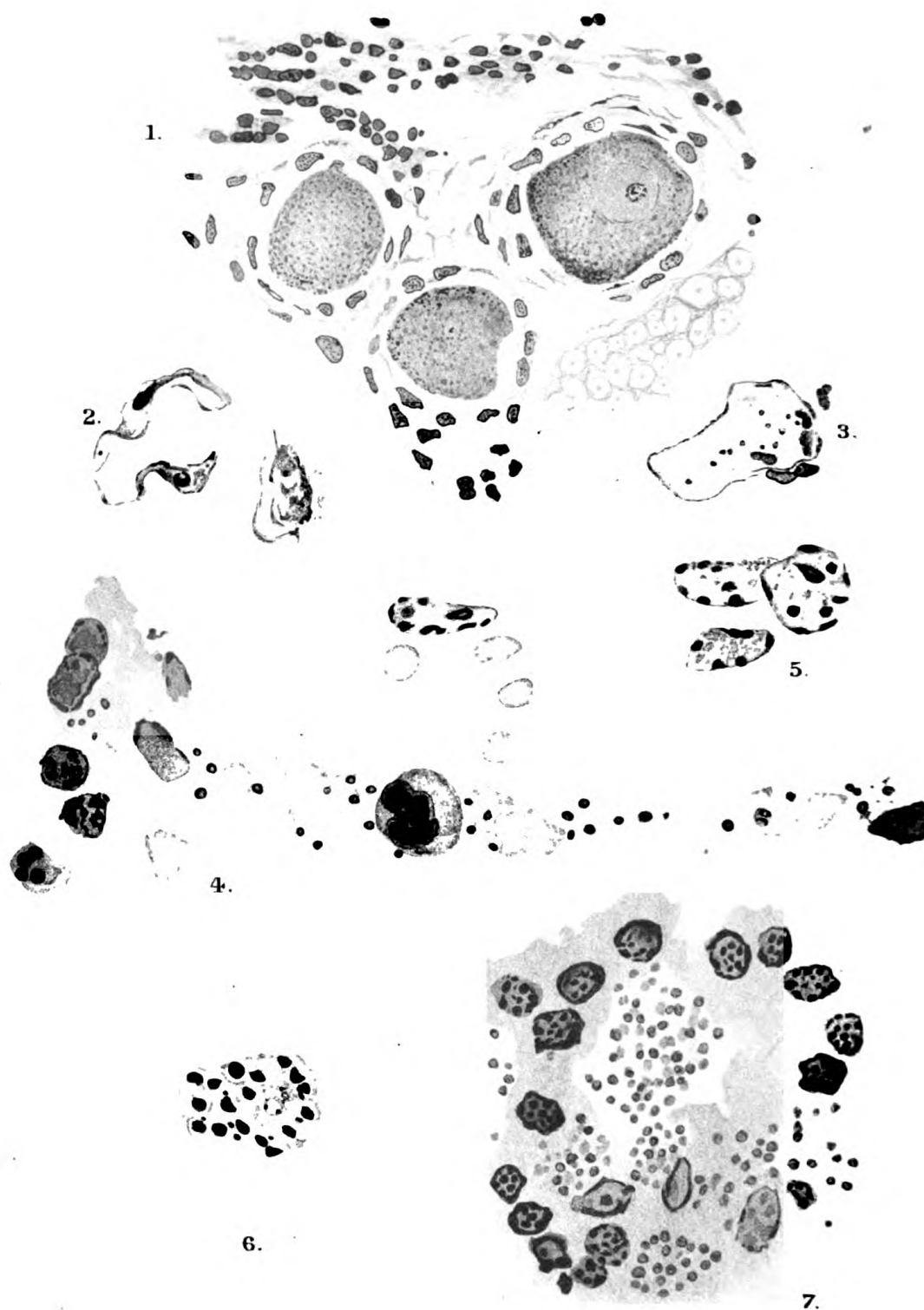


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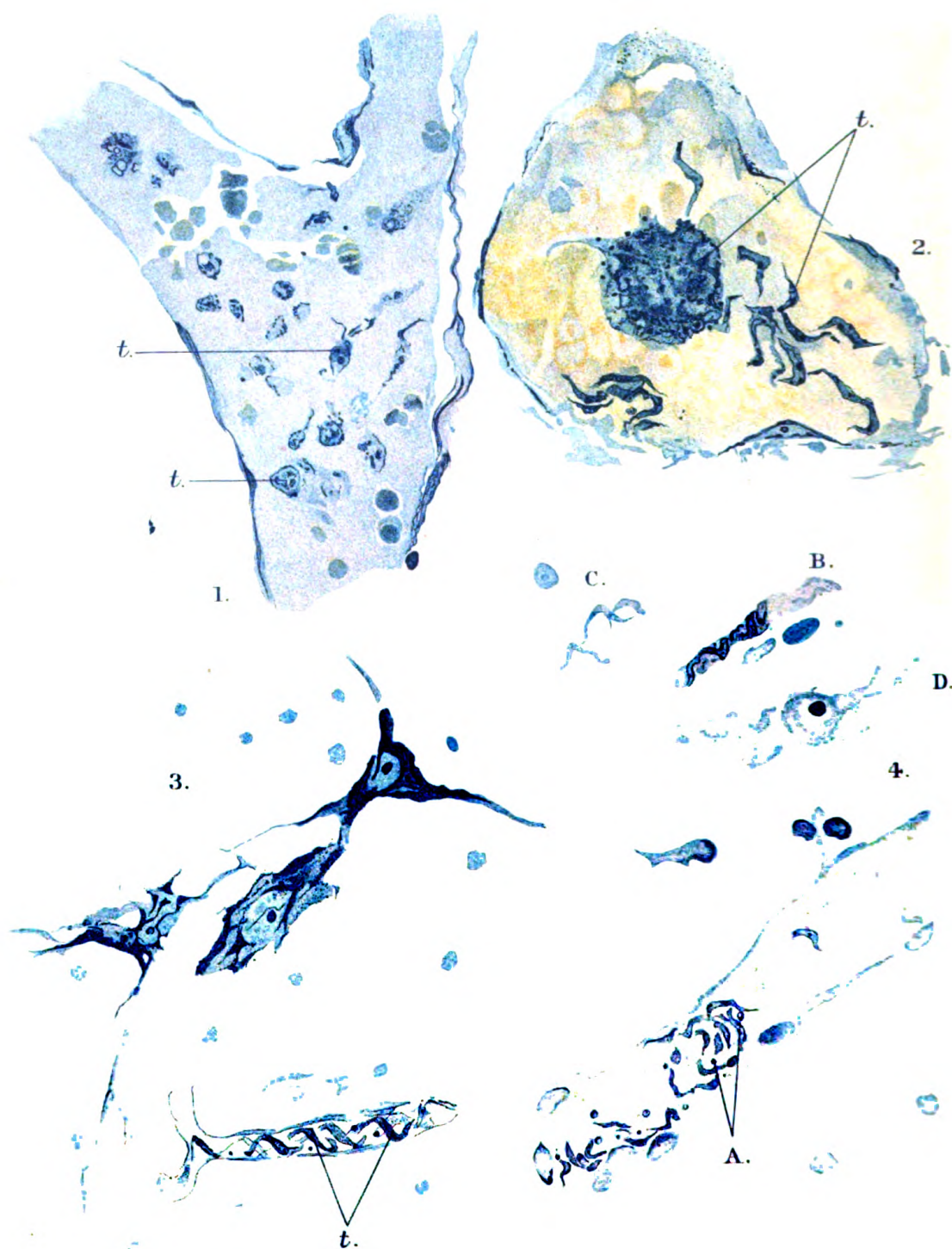


PLATE VII.

- FIG. 1.—Same section as that on Plate I., fig. 4, more highly magnified, showing endothelial cell proliferation of the capsules of the posterior spinal ganglion cells and interstitial lymphocyte infiltration. Magnification 500.
- FIG. 2.—Film preparation of *Jinga* trypanosoma in blood of infected monkey. Two trypanosomes are seen and three blood corpuscles. Beside there is a body, which appears as if fission were about to occur. Magnification 1,000.
- FIG. 3.—Transection of a vessel of brain of ox that died of *Jinga* trypanosomiasis a short time after inoculation. A large number of chromatin rings are seen. Magnification 1,500.
- FIG. 4.—Longitudinal section of a vessel of the same. Magnification 1,500.
- FIG. 5.—Bodies seen in a vessel of brain of ox. Some modified form of trypanosome? Magnification 1,000.
- FIG. 6.—Splenic blood smear, showing Leishman-Donovan bodies. Case of Kala-Azar somewhat similar appearance to 5. Magnification 1,000.
- FIG. 7.—Spleen Kala-Azar, showing Leishman bodies in the form of definite chromatin rings. Note the similarity to the appearance presented by 3, 4 and 5. Magnification 1,000. Stained by Van Gieson's method.

PLATE VIII.

- FIG. 1.—Longitudinal section of vessel of brain of ox that died of *Jinga* infection. Trypanosomes in various modified shapes are seen. Some of these may be amoeboid forms of trypanosomes; probably some are trypanosomes which have been attacked by leucocytes. Magnification 500. Stained in bulk—methylene blue and eosine.
- FIG. 2.—Small vessel of the medulla oblongata of rabbit inoculated with Surra. The animal died three months after infection. Shows a plasmodial mass in the centre and trypanosomes in a whorl near by. Magnification 1,000. Polychrome.
- FIG. 3.—Nerve cells of above, showing chromatolysis, and a small vessel with the trypanosomes (*t*) coiled up, blocking it. Magnification 1,000. Polychrome.
- FIG. 4.—Somewhat similar appearances as in fig. 2, seen in longitudinal section of vessel. Numbers of chromatin rings, probably macro-nuclei (A); (B) capillary blocked by trypanosomes; (C) trypanosomes in the tissue; (D) ganglion cell, showing marked chromolytic changes, probably due to capillary obstruction. The nucleus is swollen and clear, the body of the cell shrivelled, and there is an absence of Nissl granules. Magnification 1,000. Romanowsky.

PART II.

THE MICROSCOPIC CHANGES IN THE NERVOUS SYSTEM
IN CHRONIC DOURINE OR MAL DE COIT.

INTRODUCTION.

I am indebted to Dr. Lingard, of the Imperial Bacteriological Laboratory of India, for the nervous tissues of a number of animals dying of dourine acquired by coitus, or inoculated experimentally.

This disease, dourine, is due to a specific form of trypanosome which has the power of penetrating the mucous membrane, affects equines, and is transmitted, like syphilis, by coitus. This is of especial interest, since Schaudinn has demonstrated the *Treponema pallida* of syphilis, particularly as it seems possible that trypanosomes may undergo a spirillar modification.

It is also of interest because, like some other trypanosome infections, it may, and frequently does, run a very chronic course, and, as in the first case under consideration, more than two years may elapse before a fatal termination. Again, the lesion found in the lumbo-sacral region of the spinal cord presents some points of resemblance to a syphilitic spinal meningitis. In both diseases there is a perivascular lymphatic infiltration of the nerve roots and ganglia with lymphocytes and plasma cells, proliferation of the endothelial nuclei of the ganglia which may be intense enough to produce degeneration of the root fibres, mononuclear and plasma cell infiltration of the membranes with subpial and septal glia proliferation.

A comparative examination of the nervous tissues in this disease with that of animals infected with *Trypanosoma Gambiense*, and with the tissues of human beings dying of chronic sleeping sickness, especially those in which there was no evidence of terminal or secondary microbial infection, is of interest in showing that prolonged trypanosome infection causes in all three conditions a marked proliferation and overgrowth of the subpial, septal and perivascular neuroglia tissue. A chronic interstitial inflammation of the connective tissue structures, with lymphocyte

and plasma cell infiltration, occurs, owing to the presence of an irritative agency in the lymphatic system, which, in the case of dourine, starting in *one* seat of primary infection, extends to the inguinal glands, thence presumably by the pelvic lymphatics to the lumbo-sacral plexus and the posterior lumbo-sacral roots to the central nervous system; consequently the lower part of the spinal cord, and especially the posterior column, is first and most affected. In the case of sleeping sickness there may be any number of seats of infection, but the cervical glands are nearly always markedly involved.

Previous Observations on the Changes in the Nervous System in Dourine.

It is unfortunate that nerves of the hinder extremities were not sent, for Laveran et Mesnil¹ thus refer to the histological examination by Marck. "He showed a degeneration of the nerve fibres of the posterior columns; the other parts of the spinal cord (grey substance and other bundles of white substance) are in a healthy state. Some nerve fibres, especially on the sensory side, are degenerated at different points; the nerves of the fore-limbs are less altered. Having ascertained these facts Marck calls Dourine infective polyneuritis of the horse."

Material and notes of cases.—The following portions of the central nervous system, hardened in formol-Müller solution, were examined by various methods to display the neural and neuroglial structures: (1) Brain. (2) Spinal cord. (3) Spinal ganglia. (4) Roots of cauda equina. (5) Lymphatic glands.

The notes accompanying the tissues of Case 1 were as follows:—

An account of the Arab stallion (Monarch) will be found in the Appendices, "Report on Dourine in Different Breeds of Equines, &c.," by Alfred Lingard, M.B., M.S., D.P.H., Imperial Bacteriologist to the Government of India. Page 21.—Infective coitus occurred on May 4 to 6, 1903. Eruption of 156 cutaneous plaques between June 6, 1903, and August, 1905. Partial para-

¹ "Trypanosomes et Trypanosomiasis," p. 283.

plegia appeared February 25, 1904. The hoof of the left foot dropped off shortly before death, leaving the exposed sensitive laminae, which appeared to be atrophied. Death (836th day) August 15, 1905.

Post mortem.—A considerable quantity of gelatinous exudation was found round the lumbar portion of the spinal cord, and a smaller amount around the cervical enlargement, and a certain quantity of cerebro-spinal fluid escaped from within the membranes on removal.

The cerebro-spinal fluid did not exhibit the *Trypanosoma equiperdum* when searched for in numerous stained specimens.

Methods of Examination.—Some portions of the tissues were embedded in paraffin and sections cut 10μ thickness, and stained by the following methods:—Polychrome and Eosin, Azure Blue, Van Gieson and Leishman's stain. Other portions were embedded in celloidin and sections of 20μ thickness were cut and stained by the new Weigert method, modified Mallory and by Van Gieson's fluid. The sections by this method were thicker, but I was enabled to obtain sections of uniform thickness of the cord and membranes together with the roots, inflammatory material and attached vessels.

Description of Histological Changes in Case 1.

Throughout the grey matter of the spinal cord the ganglion cells show marked chromolytic changes, and the vessels exhibit evidence of chronic inflammation with scattered capillary hæmorrhages.

The small vessels show lymphocyte infiltration around, but there is nothing resembling the marked perivascular lymphatic infiltration met with *throughout* the grey matter in all cases of well-marked sleeping sickness. The ganglion cells for the most part retain their normal outlines, but are stained a uniform bluish-purple, with a badly defined and imperfectly stained pattern of Nissl granules. The most marked change is observed in the lumbar region.

Sections of the lumbo-sacral cord with attached roots, after embedding in celloidin and staining with Van Gieson's fluid and by the Weigert method, exhibited the following changes. The roots, anterior and posterior, are infiltrated

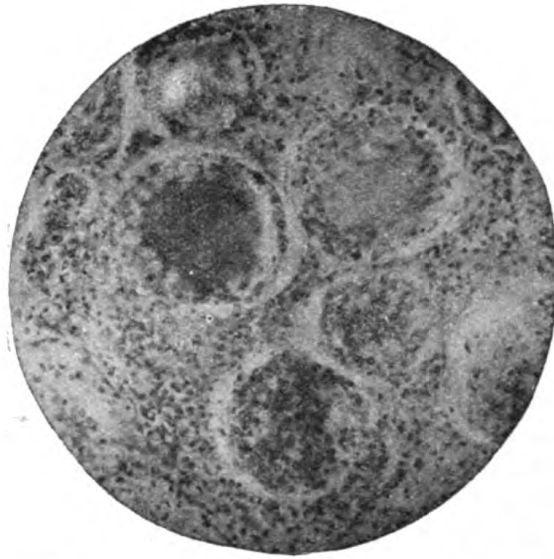


FIG. 1.—Section of posterior spinal ganglion, lumbo-sacral region. Van Gieson's stain. Showing chronic inflammatory change with atrophy and destruction of the ganglion cells. Magnification 200.

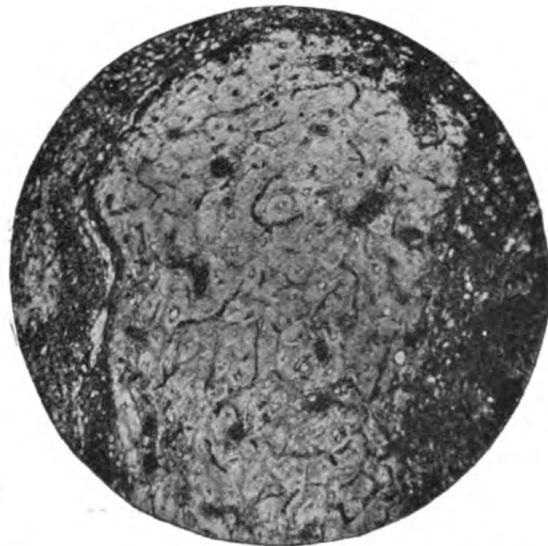


FIG. 2.—Section of posterior root of 30th segment, showing degenerative atrophy of the nerve-fibres, inflammatory change in the sheath around and proliferation of the cells of the perineurion and endoneurion. Polychrome-eosin stain. Sections $10\ \mu$ thickness. Magnification 120.

DESCRIPTION OF PLATE.

FIG. 1.—Drawing of the inflammatory exudation around 30th segment of the lumbo-sacral spinal cord, with attached membranes and roots, dourine. Stained by Van Gieson's method. Magnification $\times 230$.

R, Periphery of root with lymphocyte proliferation of very much thickened perineurion (1), the nerve-fibres appear to be intact; A, two small arteries with obliteration of lumen by inflammatory thickening of their walls, beneath there is a quantity of loose fibrous and gelatinous material with cell nuclei; G, posterior spinal ganglion cell with nuclear proliferation of the capsule and leucocytes; L, leucocytes.

FIG. 2.—Adjacent portion of the lateral column of the spinal cord, showing a leptomeningitis with great thickening of the subpial neuroglia tissue and extension of the same along the septa. Extending from the main septa are branching septa consisting of neuroglia cells. Many of these neuroglia cells, with distinct nuclei and branching processes running round and between the nerve-fibres, can be seen. In this case the noxious agent which has caused this change has operated from the sub-arachnoid space and proceeded inwards along the lymphatics of the septa.

The drawings have been made by Miss Agnes Kelly, and are faithful reproductions of the appearances presented by the specimens.



PLATE IX.

with lymphocytes, also all the vessels are surrounded and their walls infiltrated with small round cells. The connective tissue septa carrying the vessels, as well as the perineurion and endoneurion, are thickened and infiltrated with lymphocytes, also the loose connective tissue outside the dura mater; the dura mater itself and the vessels and tissues in the subdural space show signs of chronic inflammation. The condition simulates an acute syphilitic meningitis in many ways, except that I can discover only occasional evidence of an obliterative arteritis (*vide* figs. 1 and 2, plate IX.).

Some of the larger roots seen in the section (*vide* photomicrograph, fig. 2) are very markedly affected by the inflammatory process. These are judged to be posterior roots, because a posterior spinal ganglion cell can be seen here and there in them; moreover, they occupy among the roots a posterior position. The capsules of the ganglion cells that are seen, are crowded with lymphocytes presenting an appearance like that observed in sleeping sickness. Some of these roots, in transection under a high power, show the nerve fibres to have been destroyed and their place occupied by proliferated branching neurilemmal connective tissue cells lying in the centre of an oval or circular space bounded by highly vascular, thickened and swollen and amorphous endoneurion. In the centre of most of these cells is a highly refractive round or oval space.

Throughout the spinal cord, but especially at the lumbo-sacral and cervical enlargements, there is a marked thickening of the subpial network of the glia tissue, which extends into the white substance along the main septa and branches (*vide* plate IX., fig. 2).

At the periphery the proliferated glia tissue consists mainly of a dense reticulum of fibrils, but in the substance of the white matter great numbers of large branching neuroglia cells are seen sending their processes in all directions. On careful examination of the longitudinal and transverse sections these proliferated neuroglia cells, which are often spoken of as mesoglia cells, can be seen to send their processes to end like a foot upon the wall of a small vessel.

This overgrowth of glia tissue is seen throughout the white matter of the spinal cord whatever region is examined, but more especially in the lumbar and cervical enlargements, especially the former. It is more obvious in the posterior columns than elsewhere, especially along the median fissure and in the root zone. It does not *wholly* correspond to system tracts of fibres which have undergone degeneration, but appears (except in the root zone of the posterior column) to be a chronic formative proliferation of the glia tissue caused by an irritant entering the lymphatics and subarach-

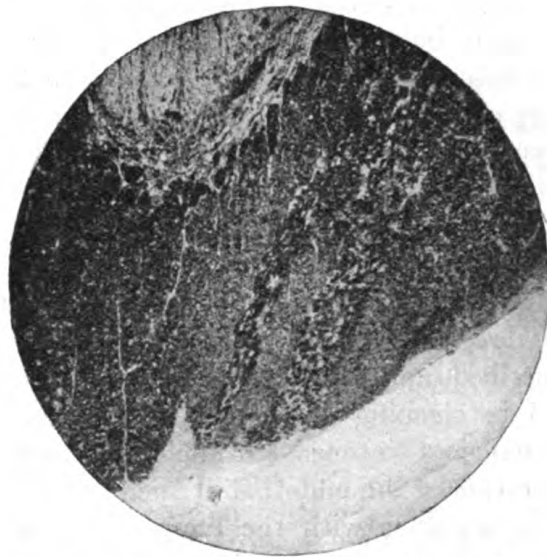


FIG. 3.—Section of the posterior column, showing three bands of degenerative sclerosis in the root zone. Weigert stain. Celloidin preparation.

noid space. The posterior column is much more affected than the rest of the white matter.

In the lumbo-sacral region there are three definite zones of degeneration in the posterior column, no doubt corresponding to the destroyed roots (*vide* photomicrograph 3). The lymphocyte infiltration is observed around the small vessels, and numerous lymphocytes are scattered about in the septa of the white matter. In the roots a well-marked perivascular infiltration with lymphocytes can be seen, and some hæmorrhages in the lumbar region. The chronic

interstitial inflammation of the anterior roots, in which all the nerve fibres appear to be normal, together with the fact that there is subpial proliferation of the glia tissue of the lumbo-sacral and cervical enlargements of their entire circumference, with the extension of the same along the septa, show that this proliferation of the connective tissue supporting structure, whether of the undamaged roots or of the spinal cord, is not due to atrophy of the nervous elements; although in the posterior columns where there are three definite bands of sclerosis, the neuroglial proliferation is, without doubt, secondary to neural destruction (*vide* photomicrograph, fig. 3). Occasional foci of microorganisms are seen, but do not play any part in the *chronic* changes above described. They are not found in the blood or inflammatory exudations. In none of the sections could I find any trypanosomes stained by the various methods which we know will show them if they are present in any numbers.

Sections of the posterior spinal ganglia and attached roots in the cervical, upper dorsal, mid dorsal, lower dorsal, and lumbo-sacral regions have been examined by the methods previously described and the appearances compared with those observed in sleeping sickness. In all these ganglia there was evidence of intense chronic inflammation with marked proliferation of the endothelial nuclei of the capsule and lymphatics, together with the lymphocyte infiltration of the interstitial fibrous tissue, and this morbid change can be followed from the nerves to the ganglion and along the posterior roots. This change is very marked in the lower dorsal and lumbo-sacral ganglia; and where the chronic inflammation is most intense, there the posterior spinal ganglion cells are most affected. In all the sections some of the ganglion cells have undergone vacuolar degeneration, and even complete destruction, their place being occupied by inflammatory products, but the neuron destruction is most marked in the lumbar region, which is the situation, as before remarked, of extensive posterior root destruction and systemic degenerative sclerosis of the posterior columns (*vide* photomicrograph, fig. 3).

Both these conditions are the outcome of the destruction of the posterior spinal ganglion cells. But this destruction must also have led to destruction of the peripheral branch of the T-shaped process of the ganglion cells, and this would give rise to a sensory polyneuritis. Unfortunately, I have not had forwarded to me any of the nerves to examine. However, the comparatively normal appearance of the anterior roots, and the very complete destruction of many of the sensory roots, together with the well-marked sclerosis of the posterior columns, would suggest that this animal may have suffered with a sensory paralysis of the hind limbs analogous to tabes dorsalis rather than a polyneuritis. An argument in favour of this hypothesis is, that in severe alcoholic and other forms of polyneuritis the motor anterior horn cells usually show characteristic degenerative changes which are not seen in the spinal cord of this animal.

Case 2.—Scarification of a minute portion of mucous membrane of left labium vaginae of a mare with a needle and inoculation of fresh blood obtained from a dourine plaque of English thoroughbred stallion Kilngarth. Appearance on twelfth day of vesicle followed by a small ulcer, which readily healed. Swelling and œdema of left labium which later involved the whole external genitals and perineal region. Vaginal mucus contained the trypanosoma of dourine. First plaque appeared on the thirty-fourth day following inoculation in the blood of which the trypanosomata were found on microscopical examination, followed at intervals during a period of 117 days by successive crops of plaques, eighty in all, which involved the skin of the body and neck, slight enlargement of the submaxillary glands, weakness, later dragging of the hind limbs whilst walking, swelling and suppuration of near hind limbs, inability to stand, destruction, necropsy: course of the disease 207 days. The cord which was forwarded was not in a fit state for examination. Several of the posterior spinal ganglia were examined and showed exactly the same change as observed in the other cases.

Case 3.—Mare covered by infected stallion Monarch, February 24, 1905. *T. equiperdum* found in vaginal mucus, March 19. May 2, No. 1 plaque appeared; *T. equiperdum* present. July 20, No. 6 plaque appeared; no further plaque observed. August 16, 1906, mare found in recumbent position; helped on to feet; walks *with uncertain action* of her hind legs and with great difficulty. August 22, 1905, death. Length of course of disease from the

first covering until death, six months. Examination of the spinal cord and posterior spinal ganglion and roots of cauda equina. There was the same endothelial cell proliferation of the capsules of the spinal ganglia with lymphocyte and plasma cell infiltration, affecting also the lymphatics of the attached posterior roots and cerebro-spinal nerves. The ganglion cells were not destroyed. There was a similar cellular hyperplasia of the endoneurion and perivascular lymphatics of the roots of the cauda equina. *Vide* figs. 4 and 5.

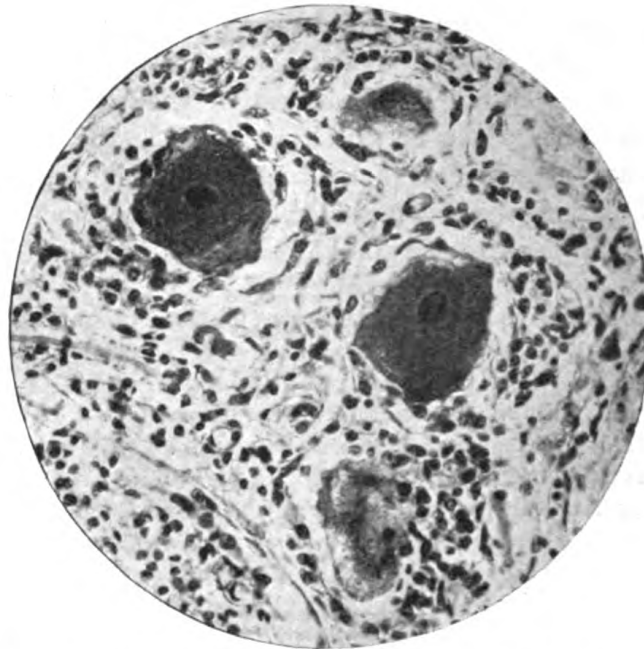


FIG. 4.—Lumbar spinal ganglion in longitudinal section, showing hyperplasia of the fixed tissue elements, namely, proliferation of the endothelial cells of the capsule and proliferation of the interstitial connective tissue cell elements and infiltration with lymphocytes. Case 3, magnification 350. Exactly the same change was found in the spinal ganglia of all the other four cases of dourine in horses examined. A less marked but quite definite change of a similar nature was found in human sleeping sickness and in syphilitic cerebro-spinal meningitis. In the latter, however, there was a more marked lymphocyte infiltration, and plasma cells were more abundant and evident.

Examination of the spinal cord showed a marked subpial and septal glial proliferation, with considerable subpial felting and infiltration of the soft membranes with mononuclear cells. There was more glia formation in the posterior columns than elsewhere, *vide* fig. 6, but it was universally increased. There was a secondary sclerosis less marked than in the first case in the root zone

and posterior median column. But throughout the posterior columns were an immense number of acutely degenerated fibres. *The condition of the posterior columns of the cord would account for the uncertain gait of the hind legs.*

Case 4.—Australian mare, aged 12 years, May 2, 1905, covered by Sangli (Dourine). July 6, 1905. Muco-purulent discharge from the vulva and vagina. July 15. *T. equiperdum* found in vaginal mucus. November 5, 1905. Lame left hind leg. March 6, 1906. Killed.

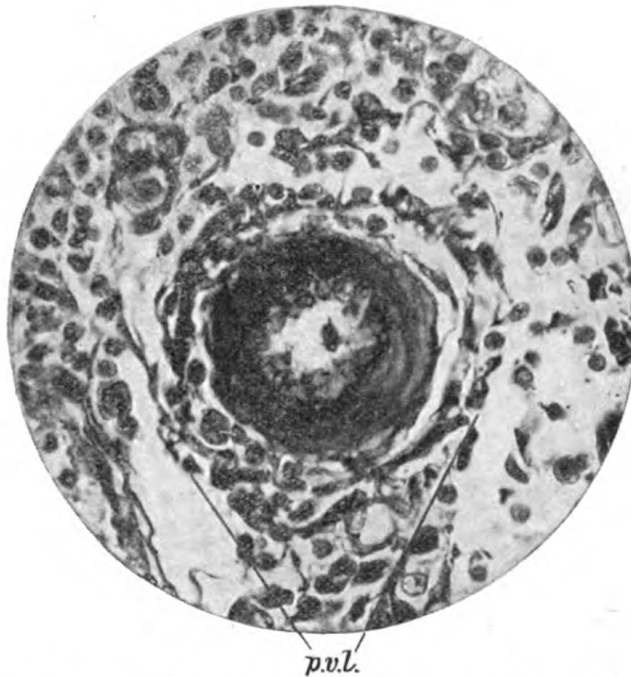


FIG. 5.—Transection of the cauda equina and conus medullaris. The photomicrograph of some of the interstitial connective tissue between the nerve root bundles. A small artery, with its perivascular lymphatic (*p.v.l.*) is cut transversely. There is a chronic inflammatory proliferation of the fixed tissue elements, consisting of lymphocytes, plasma cells, fibroblasts, and branched connective tissue cells exactly similar to the interstitial changes in the spinal ganglion. Magnification 430.

Posterior column of spinal cord showed a naked-eye sclerosis, and the posterior spinal ganglia showed the same change as the others. Sections were stained by Giemsa stain and examined. The spinal ganglia, cerebro-spinal nerves and roots attached to the ganglia, exhibited marked changes of the lymphatic structures.

The lymphatics of the nerves, especially the perivascular lymphatics, showed proliferation of the endothelial nuclei, and a bud-

ding off of mononuclear cells in which the nucleus is stained deep blue; the surrounding more or less thin zone of cytoplasm is stained pink; these mononuclears are rather larger than the lymphocytes seen in the blood—they resemble more often the large mononuclears; but they vary in size considerably in different situations. They can be seen in all stages up to the formation of the typical plasma cells of Marscholko.

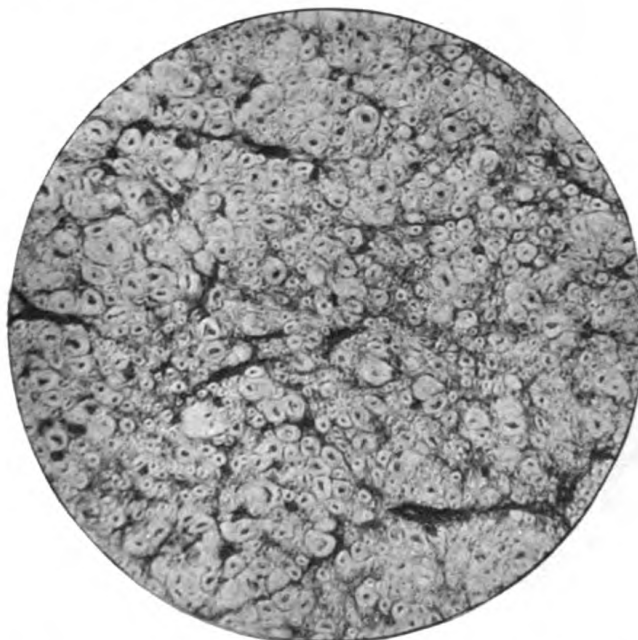


FIG. 6.—Section of the posterior column of Case 3. The section shows a diffuse subpial septal neuroglia proliferation (only the latter is shown); it was not limited to the posterior column, the whole spinal cord was affected, and is exactly similar to that seen in sleeping sickness. It is due in part to a formative connective tissue hyperplasia and in part to replacement of destroyed or atrophied nerve fibres, which the photomicrograph shows are greatly diminished in numbers and replaced by dark greyish-branching neuroglia cells. Magnification 120.

The view I take of this process is, that following the primary sore there is inguinal gland enlargement then general gland enlargement. The virus is conveyed along the lymphatics of the pelvic plexus of nerves to the lumbo-sacral ganglia primarily, and to all the spinal ganglia eventually.

With regard to the plaques in Dourine containing large numbers of trypanosomes, it is probable that the angio-neurotic oedema (which I have indicated, may be directly excited by the intense irritation of the posterior spinal ganglia) favours the

migration of the trypanosomes through the blood-vessels of the particular area of the skin affected. Having passed through the vessel wall, the accounts of Dr. Lingard seem to indicate that they modify, multiply and eventually disappear, in all probability destroyed by the active hyperplasia of the cell structures invaded. The reaction, however, may have been so intense as in some instances to terminate in leucoplacia.

The Possible Relationship of the Eruption to the Spinal Ganglia Changes.

It has been shown by numerous authorities, but especially in a very systematic manner by Head and Campbell, that herpes zoster is caused by an inflammation of the posterior spinal ganglia, the seat of the eruption depending upon the particular segmental ganglion, or ganglia, affected. It is, therefore, reasonable to associate the eruption of the characteristic cutaneous plaques with the inflammatory irritation of the ganglia as they become successively affected by the noxious agent. Both Lingard and Laveran remark upon the curious nature of the eruption: the former believes it to be an angio-neurotic oedema which occurs in the form of circular plaques, as if a ring had been introduced under the skin. They remark that although trypanosomes can only be found in the blood with difficulty, yet they are always present in the fluid which can be drawn from a plaque. Lingard concludes, therefore, that embolism by trypanosomes is the cause, but if there is an angio-neurotic oedema occasioned by the irritation of the posterior spinal ganglia, then it is possible that in the blood or the inflammatory exudation the trypanosomes may find suitable conditions for multiplying. The theory which I have advanced for the origin of the rash finds some support, moreover, in experiment, for Dr. Bayliss has shown that stimulation of the posterior roots produces vaso-dilation. Again, these plaques often leave patches of leucoplacia, which may be due to neurotrophic causes associated with the destruction of numbers of the spinal ganglion cell neurotrophic centres.

In chronic trypanosome infections by *T. Gambiense*, even

before the lethargy occurs, outbursts of irritative papules or other skin eruptions occur, and they might be accounted for by irritation of the neurotrophic centres in the spinal ganglia. The changes in the ganglia are never so intense as in Dourine, but I have now examined quite a number of posterior spinal ganglia in Sleeping Sickness cases, and I generally find some change, never sufficient, however, to produce cell destruction, such as is found in Dourine. The most intense change I have met with, is shown in Plate VII., fig. 1, and this in no way differs, except in degree, from that seen in Dourine.

Laveran and Mesnil mention that dislocation and fractures may occur in Dourine, and we know that spontaneous dislocation and fractures are met with in *tabes dorsalis*, a disease in which the posterior roots and posterior columns of the spinal cord undergo degenerative atrophy.

The tissues of a number of other animals were forwarded by Dr. Lingard, including the lymphatic glands and spinal cords of two dogs, infected by the blood of a horse suffering with Dourine, also the central nervous systems of animals dying of Surra. I have not had time to examine these tissues, but it may be of interest to state that I did not find the cell proliferation of the posterior spinal ganglion in the following case of Surra that I have examined.

Equine Surra (course of disease forty-one days).—Country-bred mare, aged 4 years, March 28, 1905, inoculated subcutaneously on the left side of the neck with 0.5 cc. of blood drawn from the jugular vein of pony, the blood of which was swarming with trypanosomes at the time of inoculation. Period of incubation four and a half days.

Course of disease.—One paroxysm only, lasting from April 2 to May 12, 1905. Death.

Dog III.—Puppy, aged 2 months, inoculated in left inguinal region with 5 cc. of blood drawn from jugular vein of a horse suffering with Dourine in the plaque stage. No rise in temperature until April 3, 1906. Death, April 11, 1906. No trypanosomata (*T. equiperdum*) observed at any time.

Dog IV.—Puppy was inoculated with 42 cc. from heart-blood of Dog III.

Although no trypanosomata could be observed in the blood at any time, the animals exhibited progressive marasmus, and died.

The brain, spinal cord and lymphatic glands of Dog III. were sent, and the following changes were found.

The lymphatic glands examined were the inguinal, mesenteric, thoracic and axillary. All showed active proliferation of lymphocytes in the germ centres, and immense numbers of large round cells in the lymph cords and sinuses, also proliferating endothelial cells forming lymphocytes and plasma cells. Many of these, especially

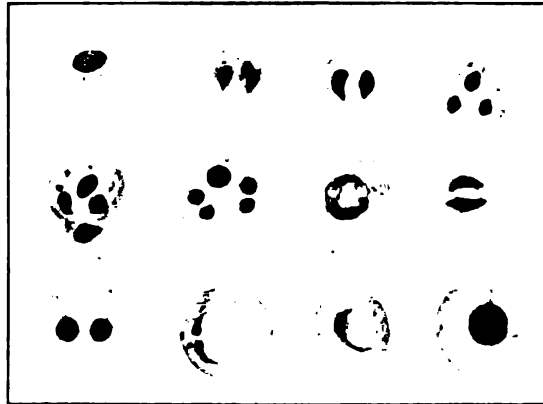


FIG. 7.—Different forms of atypical nuclear division of large mono-nuclear cells found in lymphatic structures in trypanosoma infections. Magnification $\times 500$. Staining, polychrome and eosin, hæmatoxylin and eosin.

in the inguinal gland, showed very marked nuclear changes, indicative of rapid nuclear division and proliferation, *vide* fig. 7. Professor Minchin was kind enough to examine a specimen of this gland, and he could find no evidence of the existence of protozoa. Similar cellular changes can be observed in the meningeal and perivascular infiltration of chronic sleeping sickness, and I have found them in syphiloma. They appear to be various phases in the formation of large and small mono-nuclear cells; they appear to be developed from the endothelial cells.

The central nervous system.—The spinal cord, spinal

ganglia, and brain showed no changes, except marked vascular congestion and capillary hæmorrhages into the grey matter, especially of the anterior horns of the spinal cord.

Examination of the posterior spinal ganglia in Dourine cases shows that the round celled infiltration is the result of the proliferation of the nuclei of the endothelial plates of the connective tissue cells.

The especial interest of this disease is that it presents many points of similarity to syphilis, in its protozoal origin, in its mode of transmission, in its incubation period, polyadenitis, eruptions of the skin, and histological changes, especially in the nervous system.

An account of Case 1 was published in the "Proceedings of the Royal Society," B. Vol., 78/06.

BIBLIOGRAPHY.

- LINGARD. "Report on Dourine in Different Breeds of Equines." Calcutta : Office of the Superintendent of Government Printing.
- LAVERAN ET MESNIL. "Trypanosomes et Trypanosomiasis."
- HEAD AND CAMPBELL. "The Pathology of Herpes Zoster and its Bearing on Sensory Localisation." *Brain*, 1900.
- BAYLISS. "On the Origin from the Spinal Cord of the Vaso Dilator Fibres of the Hind Limb, and on the Nature of these Fibres." *Journal of Physiology*, vol. xxvi., p. 173. 1901.

DAS VERHALTEN DER NEUROGLIA BEI NEGROLETHARGIE.

VON GEORG EISATH.

Pathological Laboratory of the London County Asylums, Claybury.

Es war mir durch die Güte von Dr. Mott, Director des Laboratoriums, ermöglicht, einen Teil des reichlichen Materials, welches ihm durch Col. Bruce (Director of the Sleeping Sickness Commission of the Royal Society) zu histologischen Untersuchungen zur Verfügung gestellt worden war, hinsichtlich der krankhaften Veränderungen der Neuroglia genauer zu studieren.

Die Negrolethargie wurde vom *histopathologischen Standpunkte* aus von Mott in Jahre 1899 gründlicher behandelt. Ferner lieferten histologische Mitteilungen Sarmiento und Franca sowie Valente. Die portugiesische Forschungs-expedition behandelte die Schlafkrankheit auch vom histologischen Gesichtspunkt aus. Alle genannten Arbeiten stimmen eindeutig darin überein, dass die histologische Grundlage der Negrolethargie gebildet wird von einer Meningo-Encephalo-Myelitis und zwar, wie übereinstimmend mitgeteilt wird, aus folgenden Gründen: Die Krankheit beginnt mit Fieber und trägt den Charakter eines infectiösen Leidens. An der Leiche trifft man die Meningen verdickt und mit Leukocyten infiltrirt. In der Gehirns- substanz finden sich allenthalben vom Blute herstammende Lymphocyten und Plasmazellen die besonders in der Umgebung der Gefässe ausgedehnte Infiltrate bilden. Aber auch das Parenchym der Rinde, die pericellulären Räume der Ganglienzellen und selbst das Geflecht des Nervengewebes sei von reichlichen Lymphocyten besetzt.

Wenn man im Besonderen ins Auge fasst, was über das Verhalten der *Neuroglia* bei Negrolethargie bis nun berichtet

wurde, gewinnt man den Eindruck, dass dieses wichtige Gewebe nicht in der gebührenden Weise beachtet wurde, denn die mehrfach genannten portugiesischen Rapports bringen über die Veränderungen der Glia bei Schlafkrankheit folgende ganze Mitteilung: "Dans le tissu interstitiel il y a toujours une infiltration par des leucocytes et des plasmazellen. Ces éléments sont épars dans toute l'étendue du stroma du ganglion; les plasmazellen s'accumulent de préférence autour des vaisseaux, mais on trouve souvent, loin de ceux-ci, des foyers constitués presque exclusivement par ces éléments." Ferner sagte Mott in einem Vortrage vor ungefähr einem Jahre, dass bei Sleeping Sickness beträchtlich Gliawucherung zu beobachten ist. Soviel wurde in der mir zugänglichen Literatur bis jetzt hierüber veröffentlicht. In einer neuen Arbeit, welche Mott über Negrolethargie zu veröffentlichen im Begriffe steht, konnte er der Neuroglia nicht die nötige Aufmerksamkeit schenken. Er beschränkte sich darauf festzustellen, dass bei Schlafkrankheit eine starke Wucherung der Glia zu beobachten ist, und stellte sein Material mir zu einer eingehenden Untersuchung der Glia zur Verfügung. Ich unterzog mich dieser Arbeit um so lieber, als mir darum zu tun ist, eine neue Gliafärbung, die ich an anderer Stelle veröffentlichen werde, auf ihre Leistungsfähigkeit zu erproben.

Bevor auf die Beschreibung der Gliaveränderungen eingegangen wird, ist es zum Verständnis derselben nötig, voraus zu schicken, dass mit der Färbung, die ich anwende, nicht nur die Kerne und Fasern wie bei der electiven Gliafärbung Weigerts dargestellt werden, sondern auch die Gliazellkörper. Diese sind teils rund, teils mit Fortsätzen versehen. Nebenbei sei bemerkt, dass manche Gliazellen durch das Mallorysche Haematoxylin, das in Anwendung kommt, im Körper bläulich gefärbt, während viele Gliazellen nur in den Umrissen ihrer weissen Zellkörper sichtbar gemacht werden. Die Färbung ist demnach nicht eine vollkommen tinctorielle, sondern zum Teile nur eine bildlich darstellende. Die Gliazellen sind nach Obigem einzuteilen (1.) in solche, die einen runden Zellkörper besitzen und (2.) in solche, deren Zellkörper Fortsätze haben. Die Fortsätze der Gliazellen sind

nicht immer von gleicher Beschaffenheit sondern weisen zwei verschiedene Formen auf u.zw. (a) Fortsätze, welche protoplasmatischer Natur sind, das heisst solche, in welchen nur das Protoplasma des Zelleibes in Zacken ausläuft, (fig. 5, a) und (b) in solche Fortsätze, die wirkliche Fasern im Sinne Weigerts besitzen. Diese Weigertschen Fasern aber sind nicht frei liegend, sondern werden, wie bereits Held beobachtete, vom Protoplasma der Zellausläufer eingeschleitet.

Es sind die runden und mit Fortsätzen versehenen Gliazellen über das ganze Centralnervensystem ausgestreut, und es finden sich nach dieser neuen Gliafärbung, so weit bisher beobachtet wurde, im normalen Hirn-Rückenmark keine Stellen, in denen nur runde Gliazellen vorkommen, wie das Weigert z. B. von den Schichten der Ganglienzellen des Grosshirns annahm, sondern die runden und die mit Fasern ausgestatteten Neurogliazellen liegen auch in der normalen Grosshirnrinde gleichmässig verbreitet herum. Allerdings sind die meisten Gliazellen der Rindenschichten, so weit sie Fortsätze besitzen, nur mit protoplasmatischen Ausläufern versehen und haben keine Fasern im Sinne Weigerts.

Es stehen zur Untersuchung acht Gehirne und sechs Rückenmarke zur Verfügung. Indes findet sich nicht das vollständige Centralnervensystem vor, sondern nur kleine Stücke aus der Grosshirnrinde und vom Kleinhirn, sowie bei manchen nur sehr spärliche Teile des verlängerten Markes und Rückenmarkes. Das Material ist in Formol-Müllerflüssigkeit gehärtet und 2-3 Jahre alt. Klinische Krankengeschichten stehen mir nicht zu Gebote. Die vorliegenden Mitteilungen sind sehr kurz gehalten und bringen namentlich über psychische Erscheinungen und andere Störungen des Centralnervensystems fast keine Nachrichten.

Das Material stammt von folgenden Kranken: Msubica, 7 jähriges Mädchen, gestorben an Pyaemie und Lungenentzündung nach sehr chronischen Verlauf der Negrolethargie. Sempagana, 8 Jahre alt, mit chronischem Krankheitsverlaufe. Hamesi, 12 Jahre alter Knabe, gestorben an Pleuritis. Wasiwa, 18 Jahre alt, männlich, gestorben infolge der

Schlafkrankheit ohne besondere intercurrente Krankheit. Arcade, 25 jähriger Mann, war lediglich an den Folgen der chronisch verlaufenden Schlafkrankheit zugrunde gegangen. Nonbi, Frau mit 30 Jahren, vermochte im Endstadium weder zu sprechen noch zu gehen, verstand aber die Fragen, die an sie gestellt wurden. Die Pupillen zeigten keine Lichtreaktion, einzelne Muskeln waren rigid, Harn und Kot gingen unbemerkt ab. Es fehlten die Kniesehenreflexe und der Fussklonus. Goavera, Frau mit 40 Jahren, war infolge der Schlafkrankheit gestorben. Kerongo, 40 jähriger Mann: die Krankheit hatte einen verhältnismässig schnellen Verlauf genommen. Der Tod trat lediglich als Folge der Negrolethargie ein.

Da die untersuchten Fälle im Ganzen und Grossen übereinstimmende mikroskopische Bilder geben, kann die folgende Beschreibung schon auch der Kürze und Uebersicht halber in etwa zusammenfassend gemacht werden, wobei zuerst das Grosshirn, dann das Kleinhirn und zuletzt das Rückenmark abgehandelt werden sollen.

GROSSHIRN.

Bei der Betrachtung des Grosshirns werden wir zuerst die Rinde, dann das Mark vornehmen, und in der Rinde wiederum die *oberflächliche Granularschichte* wegen ihrer besonderen histologischen Beschaffenheit von den Ganglienzellenschichten auseinander halten und eigens beschreiben. Als Musterfall wird das Kind Msubica dienen, weil bei diesem die histologischen Störungen am schwersten und ausgeprägtesten ersichtlich sind. Wir finden in diesem Falle an der oberflächlichen Granularschichte sehr auffällig vermehrte Gliazellen teils runde, meist aber solche, die mit Fortsätzen versehen sind und Weigertsche Fasersubstanz besitzen. Die hier vorfindlichen Gliazellen lagern hauptsächlich an der oberflächlichsten Zone gegen die Meningen hin, haben bald helle, bald dunkle Kerne, an denen gröbere Veränderungen nicht wahrzunehmen sind. Die Zelleiber sind vergrössert und zeigen ein üppiges, wohlgenährtes Aussehen. Die Zellfortsätze sind namentlich an der Rand-

zone ausserordentlich vermehrt und bilden gegen den subpialen Raum hin ein eng gewobenes, dichtes Filzwerk. Dieses Faserwerk besteht aus den protoplasmatischen Ausläufern des Zelleibes, die besonders an der oberflächlichsten Randzone auch reichliche Weigertsche Fasern in sich schliessen. In der Umgebung der Gefässe zieht das Gliafilzwerk auch herein bis in die Ganglienzellenschichten und ist an manchen Stellen auch begleitet von der vielfach schon von anderen beschriebenen Lymphocyteninfiltration. Der Gliafilz wird gegen die oberflächlichste Nervenzellenschichte hin immer weitmaschiger, die Gliazellen seltener, letztere sind aber hier gegenüber der Norm noch beträchtlich vermehrt. Diese histologischen Veränderungen der oberflächlichen Granularschicht haben eine grosse Aehnlichkeit mit den Gliawucherungen, welche vielfach bei der progressiven Paralyse beobachtet werden.

In der oberflächlichen Granularzone ist der Befund in allen übrigen untersuchten Fällen dem beschriebenen sehr ähnlich, nur nicht so ausgeprägt. Im einen Falle sind die Gliazellkerne vorherrschend vergrössert und hell gefärbt, in anderen mehr dunkel und wie leicht geschrumpft. Der Zellkörper verhält sich auch bei einzelnen Kranken verschieden. Während Sempagana auch in dieser Schichte dickleibige, gemästete Gliazellen mit protoplasmatischen Ausläufern hat, besitzt Arcade reichliche, aber zartere Faserung der Zellen mit vielen Weigertschen Gliafasern. Besonders hervorzuheben ist, dass bei Kerongo in dieser oberflächlichen Granularschicht eine Infiltration der Gefässlymphscheiden auch an den grösseren Gefässen nicht gefunden werden kann. Ausserdem hat Kerongo das Besondere, dass viele Gliazellen dunkle, verkleinerte Kerne und einen homogenen, blass gefärbten Zelleib besitzen, dass die scharfen Zellumrisse verloren gegangen, dass viele Ausläufer wie verkümmert sind und teilweise keinen Weigertschen Faserstoff tragen. (Fig. 5, c und d.)

Was in der oberflächlichen Granularzone in allen Fällen gemeinsam sich vorfindet, das ist eine Vermehrung der Gliazellen und eine Hypertrophie derselben.

Im Gebiete der Ganglienzellenschichten zeigt Msubica,

ERKLÄRUNG DER BILDER.

Alle Bilder stammen von Praeparaten, welche in Formol-Müllerflüssigkeit gehärtet worden waren. Die Bilder Figur 1, 2, 3, 4, 5 *a* und *b*, sind nach der eigenen Gliafärbemethode und Fig. 5 *c* *d* und *e* nach van Gieson gefärbt.

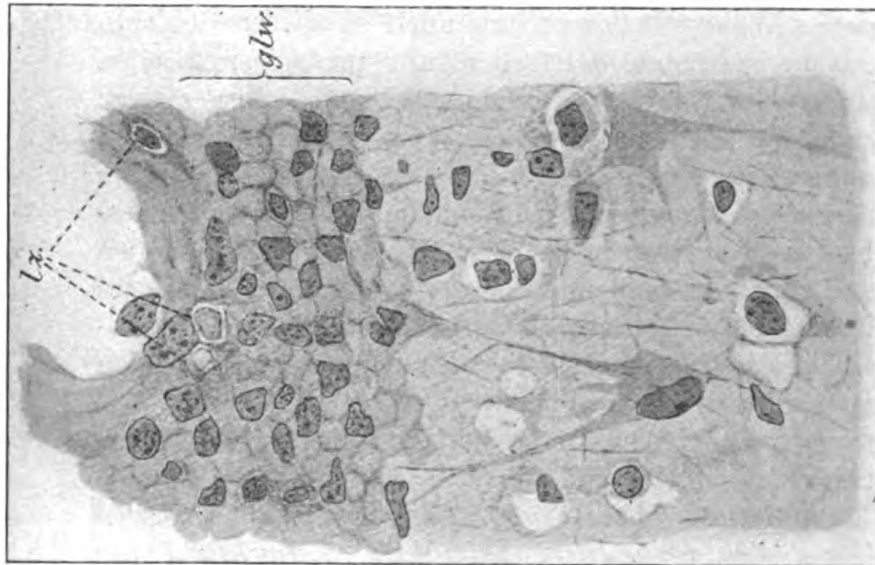


FIG. 1.

FIG. 1. Stellt ein grosses Gefäss aus dem Marke der Grosshirn dar; um das Gefäss herum deutliche Lymphocyteninfiltration (*lz*), die nur in die obersten Schichten des mächtigen Gliawalles vordringt, nicht aber die Gliawucherung durchsetzt und in das Nervenparenchym hineinreicht. (Fall Nonbi.)

FIG. 2. Kleines Gefäss aus dem Marke des Grosshirns; keine Rundzelleninfiltration und gleichwohl Hyperplasie und Hypertrophie des umgebenden Gliagewebes. (Nonbi.)

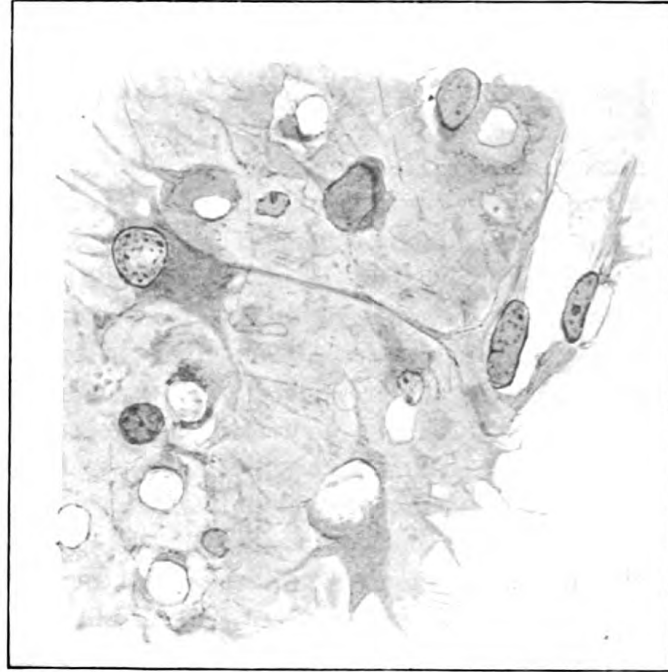


FIG. 2.

der wieder als Grundlage für die weitere Beschreibung dienen soll, abermals eine Vermehrung der Neurogliazellen. Die Zellkerne, namentlich der runden Gliazellen sind hyperplastisch und weichen in Gestalt und Färbung nicht viel von der Norm ab, ausser in dem Punkte, dass sie etwas dunkler blaue Färbung besitzen. Kernteilungsfiguren kann man nur sehr, sehr selten sehen. Die Leiber der runden Zellen sind gross, wohlgenährt, teils bläulich, teils hell weiss gefärbt, besitzen deutlich sichtbare Zellumrisse und zeigen im Übrigen normale Gestalt. An vielen Gliazellen der Ganglienzellenschichten sind Fortsätze wahrzunehmen und zumal die in den obersten Schichten gelegenen haben lange, schwächliche Ausläufer mit Weigertschen Fasern, die mit dem erwähnten Glianetze in der granulären Randschicht in unmittelbarem Zusammenhange stehen und hereinziehen bis in die Gegend des Baillarger-Gennarischen Streifens. Dieses Vorhandensein von Weigertschen Fasern in den obersten Ganglienzellenschichten bildet bei der Negrolethargie eine Ausnahme und kommt ausser in diesem Falle nur noch bei Wasiwa in geringerem Masse vor. Auch viele Gliabegleitzellen besitzen bei Msubica Ausläufer, welche sich jedoch nach allen Richtungen hin gleichmässig ausbreiten und in diesem Punkte von jenen Gliabegleitzellen abweichen, die von Alzheimer bei Dementia praecox beschrieben worden sind und die ihre Ausläufer mehr gegen die Ganglienzelle hin ausstrecken und sich an diese gleichsam festklammern, aber nach der entgegengesetzten Richtung hin keine oder nur kümmerliche Fasern schicken. Im Allgemeinen muss hervorgehoben werden, dass die grösseren, mit Fortsätzen versehenen Gliazellen undeutliche Grenzlinien zeigen und in den tieferen Schichten nur ganz wenige und zarte Weigertsche Fasern erkennen lassen. Soweit eine Gliawucherung mit Faserbildung zu beobachten ist, hält sie sich an die Gefässe und an die nächste Umgebung der Ganglienzellen; in letzterem Falle hat man es mit gewucherten Gliatrabantzellen zu tun. Besonders hervorzuheben ist, dass selbst bei Msubica in der Markleiste keine diffuse Gliavermehrung wahrgenommen werden kann, wie solche bei der Paralyse zumeist vorfindlich ist. Zum

Teile in der Nähe der Gefässe, zum Teile aber auch entfernt und unabhängig von diesen finden sich eigentümliche Gebilde, welche das Haematoxylin nicht aufnehmen, zu meist eine kugelige oder länglich eiförmige Gestalt und die Grösse einer grossen, runden Gliazelle besitzen, manchmal oberflächlich ganz glatt, manchmal jedoch mit seichten Furchen und Buckeln behaftet sind. Diese sonderbaren Gebilde sah bereits Mott und beschrieb sie als Körnchenzellen. Es soll hier hervorgehoben werden, dass in diesem sehr vorgeschrittenen, chronischen Fall auch im Gebiete der Nervenzellschichten sich einzelne Gefässe mit Lymphocyteninfiltration beobachten lassen, während dagegen die Mehrzahl namentlich der kleineren Blutgefässe eine Rundzelleninfiltration nicht besitzt. Trotz eifrigen Suchens bin ich nicht in der Lage, abseits von den Gefässen mit Sicherheit im Parenchym Lymphocyten zu sehen, ebenso wie in den pericellulären Räumen nirgends vom Blute herstammende Rundzellen, sondern immer nur Neurogliazellen gefunden werden können. Die schichtenförmige Lage und Anordnung der Ganglienzellen ist nicht gestört.

Im Ganzen und Grossen stimmen die übrigen Fälle, ausgenommen Kerongo, mit obiger Beschreibung überein, nur dass die Veränderungen in geringerem Masse vorhanden sind. Sehr bemerkenswert ist, dass in der Mehrzahl der Fälle die Umrisse, namentlich jener Gliazellen, die Fortsätze tragen, sehr verwaschen und unklar sind und gegenüber den relativ scharf abgegrenzten Gliazellen in der normalen Rinde nur schwer und undeutlich zu sehen sind.¹ Die protoplasmatischen Fortsätze der Neurogliazellen sind von noch undeutlicheren Grenzlinien und ungemein schwer mit dem Auge wahrzunehmen, obzwar sie nicht selten verdickt und im Volumen etwas vergrössert sind. In den Schichten der Ganglienzellen kommen bei den übrigen Fällen nur selten Blutgefässe mit Lymphocyteninfiltration vor, was wohl darauf zurückzuführen ist, dass von der Krankheit diese Schichten am längsten verschont bleiben.

¹ Ob dieser Befund eine wirkliche, der Negrolethargie zukommende Eigentümlichkeit der Gliazellen darstellt oder aber eine Folge dessen bildet, dass das Material erst so spät verarbeitet wird, kann nicht entschieden werden.

Wie Kerongo schon oben seine Besonderheiten zeigte, so ist das auch im Gebiete der Ganglienzellenschichten der Fall. Die Glia ist nur unansehnlich vermehrt. Die Gliazellkerne sind zumeist dunkel bläulich gefärbt, sonst von gewöhnlicher Grösse und Form. Worin dieser Fall aber am meisten von den übrigen verschieden ist, beruht darin, dass die protoplasmatischen Fortsätze der Gliazellen, welche Fortsätze in den normalen Rindenschichten mit der von mir angewandten Färbung ganz deutlich sichtbar gemacht werden können und auch in den anderen, oben beschriebenen Fällen von Negrolethargie noch mit Mühe zu beobachten waren, ihre Färbbarkeit vollends verloren haben und nicht mehr dargestellt werden können. Eine Erklärung für dieses ganz sonderbare Verhalten der Glia kann vorderhand nicht gegeben werden, so lange man nicht weiss, ob dieses Unsichtbarwerden der Gliazellfortsätze der Gliawucherung und Bildung von Weigertschen Fasern vorausgeht oder nachfolgt, d. h. ob diese Veränderung zur progressiven oder regressiven Phase der Zellveränderung gehört. Hierüber müssen uns erst weitere Beobachtungen Klarheit bringen. Im vorliegenden Falle ist wohl die Annahme berechtigt, dass die Gliazellen hier einer Veränderung entgegen gehen, welche wir später kennen lernen werden, nämlich der Hyalinentartung.

Die Befunde im Gebiete der *Ganglienzellenschichten der Grosshirnrinde* weichen von einander ab und sind nicht so übereinstimmend wie in der Granularschichte. *Was allen Fällen gemeinsam ist, macht nur sehr wenig aus und besteht darin, dass die Gliazellen im Allgemeinen numerisch etwas vermehrt sind.*

Die pathologischen Veränderungen im *Marke des Grosshirns* bestehen bei Msubica darin, dass eine ganz enorme Vermehrung der Gliazellen namentlich in der Nachbarschaft der Gefässe sich vorfindet. Die Kerne der runden Gliazellen sind von normaler Beschaffenheit, teils dunkel, teils hell gefärbt (Fig. 1 und 2). Die Kerne der gefaserten Gliazellen befinden sich zum grossen Teile in äusserster Schwellung, sind glänzend hell und zeigen nur spärliche Granulierung. Andere sind von eiförmiger Gestalt, wieder

andere besitzen Einschnürungen und Einkerbungen der Oberfläche. Noch andere besitzen dunkel blaue Färbung und bieten ein Aussehen, wie wenn sie geschrumpft und eingetrocknet wären. Die Kerne liegen zum Teile ganz an den äussersten Rand des Zelleibes gedrängt (Fig. 2). Der Körper der runden Gliazellen weist ausser Erscheinungen von Hypertrophie nichts Bemerkenswertes auf. Dagegen sind die Gliazellen mit Fortsätzen, in der Umgebung der Gefässe zumal, ausserordentlich vermehrt und in dichten Gruppen angehäuft und zeigen an ihrem Körper ganz auffällige Veränderungen. Hier kommt so recht der Charakter der Gliazelle bei Negrolethargie zum Ausdruck. Während die normalen Zellen scharfe Zellgrenzen und zarte, dünne Ausläufer tragen (Fig. 5a), zeigt sich bei Negrolethargie der Gliazellkörper vergrössert und mächtig geschwellt wie in vollendetem Mastzustande. Die Zellumrisse sind undeutlich, die Ausläufer vielfach kurz und verwaschen (ähnlich der grossen Gliazelle in Fig. 2 vom Falle Nonbi); nur sind bei Msubica die Zellen noch grösser, dicker und plumper und tragen kurze nicht scharf abgegrenzte, protoplasmatische Fortsätze. Das sind so recht die Charakterzeichen einer Gliazelle bei Schlafkrankheit. Viele Neurogliazellen zeigen ein fast homogenes glasiges Aussehen. Neben diesen Veränderungen sind einzelne Zellen in körnigem Zerfalle, andere in atrophischer Schrumpfung begriffen.

Die Blutgefässe des Markes besitzen, nebstdem dass sie von stark gewucherter Glia umgeben sind, häufig auch eine dichte Lymphocyteninfiltration u. zw. sind es meistens die grösseren Gefässstämme, an welchen die Infiltrate liegen, während an den kleineren Gefässen Rundzelleninfiltrate viel seltener sind. Entfernt von den Gefässen können unter den sicher erkennbaren Zellen Lymphocyten nirgends aufgefunden werden. Dagegen sind die oben beschriebenen Schollen (Körnchenzellen) im Marke herum allenthalben zerstreut vorfindlich.

Die übrigen Fälle, ausgenommen Kerongo, und selbst dieser in vielen Stücken, stimmen mit dem vorbeschriebenen überein. Es ist jedoch notwendig den Fall Nonbi (von

welchem Fig. 1 u. 2 stammen) einer genauen Betrachtung zu unterziehen. Fig. 1 zeigt uns den Ausschnitt eines grösseren Gefässes mit dessen nächster Umgebung. Oben ist annähernd in einem Halbkreise die verdickte, homogene Gefässwand zu sehen. Daran schliesst sich eine Zone massenhaften Zellinfiltrates, das in Wirklichkeit noch viel dichter ist, als die schematisch gehaltene Zeichnung darstellt. Dieses Infiltrat besteht aus zweierlei Zellen, aus Lymphocyten und Gliazellen. Die Lymphocyten liegen im perivaskulären Lymphraum am dichtesten in der nächsten Nähe des Gefässwand, ziehen aber auch weiter in das maschenförmige zarte Netzwerk der Gliafasern hinein. Die Gliazellen mit ihren Fasern bilden um das ganze Gefäss herum gleichsam einen breiten und dichten Wall (Fig. 1 glw), der offensichtlich den Zweck hat, das Nervengewebe von der Einwanderung der Leukocyten zu schützen. Dieser Gliawall erfüllt, so weit wenigstens als ich wahrnehmen kann, tatsächlich diesen Zweck, denn es ist nicht gelungen, ausserhalb des erwähnten Glianetzwerkes, d. h. gegen das Nervengewebe hin je Lymphocyten zu treffen. Diese befinden sich wohl im perivaskulären Lymphraum, dringen auch in das Maschenwerk des Gliawalles ein, sind aber nicht imstande, diesen zu durchsetzen und in das Nervengewebe auszuwandern. Ausserhalb des Gliawalles befindet sich nur hypertrophisch gewuchertes Neurogliagewebe. Die Gliawucherung hat hier Grund und Ursache genug; denn sie bewahrt das Nervengewebe von dem Eindringen von störenden Fremdkörpern, als welche die Lymphocyten ja anzusehen sind.

Ganz anders liegt aber die Sache bei Fig. 2, die ebenso von der Nonbi stammt. Hier ist ein kleineres Gefäss mit verdickten Endothelzellen dargestellt. Obgleich von einer Lymphocyteninfiltration noch nichts bemerkt werden kann, ist doch die Neuroglia in Wucherung begriffen, was daraus hervorgeht, dass die Zellelemente vermehrt und hypertrophisch sind, ja teilweise sogar schon in einer regressiven Metamorphose sich befinden. Keine weissen Blutkörperchen sind hier im Gewebe vorfindlich sondern nur vermehrte, wohlgenährte, vergrösserte Gliazellen. Die grosse Zelle,

die den Fortsatz gegen das Gefäss hin streckt, hat einen abnorm grossen Zellkern und einen Leib, der schon nicht mehr ganz scharfe Umrisse besitzt. Eine andere ver-

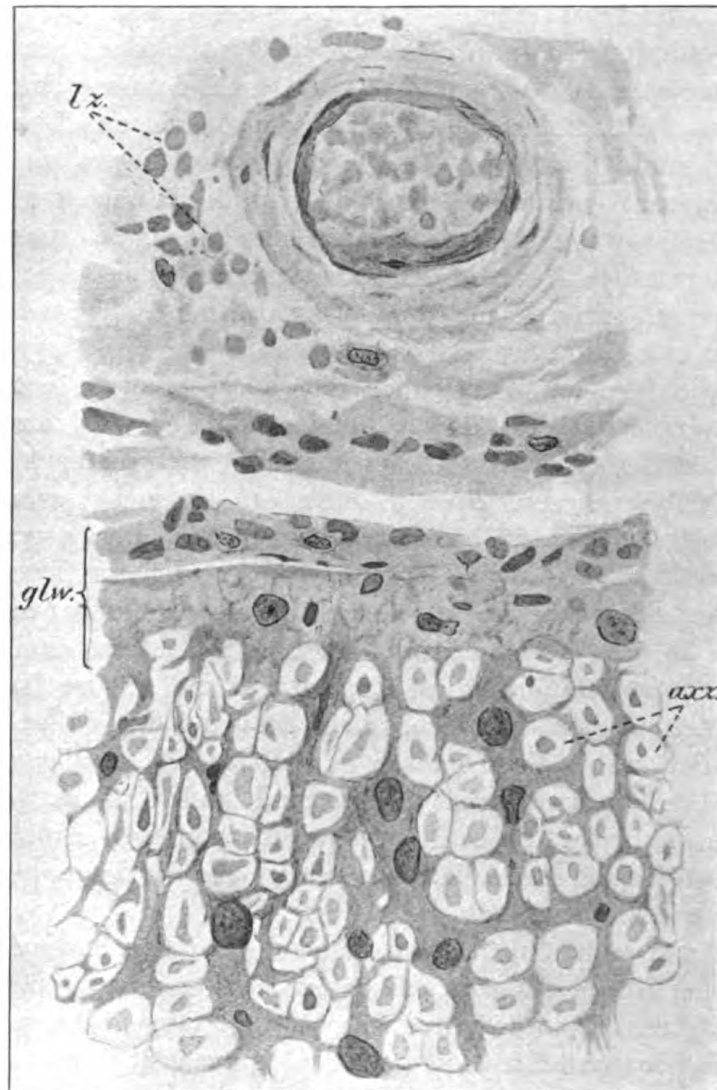


FIG. 3.

Oberfläche des Rückenmarkes mit ausgebreiteter Lymphocyteninfiltration (*lz*) und starker Gliawucherung (Gliawall) von Arcade.

grösserte Zelle, die rechts am Rande liegt, zeigt einen eiförmigen, in äusserster Schwellung befindlichen hellen, ganz wandständigen Kern und der Zelleib mit den proto-

plasmatischen Fortsätzen ist bereits von nicht mehr ganz scharfer Umgrenzung. Nebstdem sieht man vermehrte protoplasmatische Gliafasern in der Nachbarschaft des Gefässes. Von so reichlichen und vergrösserten Zellen und so vermehrten Gliafasern wäre unter normalen Verhältnissen das dünne Gefäss sicher nicht umgeben. Dieser Befund ist für das Verständnis des Krankheitsprocesses von besonderer Wichtigkeit und wir werden später noch einmal darauf zurückkommen müssen.

Als besondere Eigentümlichkeit im Verhalten der Glia im Marke des Grosshirns wäre hervorzuheben, dass bei Wasiwa sehr viele grosse Gliazellen sich finden, welche dicke, teils spiralige, teils meanderlinienartig gebogene protoplasmatische Fortsätze tragen. Es finden sich aber auch einzelne Zellen, welche, wie Bild 5 b darstellt, sich in regressiver Umänderung befinden, geschrumpft aussehen, kleine, seichte Einkerbungen an der Oberfläche des Körpers zeigen und schmale, dünne Ausläufer haben. Das Protoplasma ist lebhaft blau gefärbt und schliesst in sich neben dem Kern auch ein bläschenartiges Gebilde. Der Kern selbst ist dunkel gefärbt und geschrumpft. Bemerkenswert ist, dass bei Hamesi keine homogenen Schollen (Körnchenzellen), wohl aber verdickte, auf Hyalinentartung verdächtige Gefässwände beobachtet werden.

Um noch einiges über das Verhalten der Glia bei Kerongo mitzuteilen, sei bemerkt, dass hierbei an vielen Stellen eine deutlicher Vermehrung derselben nicht festgestellt werden kann. An anderen Stellen dagegen u. zw. namentlich in der Umgebung der Gefässe ist die Gliawucherung mit deutlicher Vermehrung der Zellen und der protoplasmatischen Fortsätze sehr beträchtlich. Hier finden sich zumal in den grossen Zellen mit Fortsätzen deutliche Kernveränderungen. Die Kerne sind meist dunkel gefärbt, besitzen Einbuchtungen und in seltenen Fällen förmliche Einschnürungen, andere Kerne sind dunkel gefärbt und geschrumpft, atrophisch. Ein ganz eigenes Verhalten bieten die grossen Gliazellen, welche Ausläufer besitzen. Die Leiber dieser Zellen schliessen zumeist dunkel blaue geschrumpfte Kerne in sich und haben ein Protoplasma, das

ganz homogen glasig aussieht und keine deutlichen, scharf geschnittenen Zellumrisse mehr zeigt. Die protoplasmatischen Fortsätze sind nur schwer, an vielen Zellen nur mehr andeutungsweise zu sehen. Diese Zellen nehmen das Haematoxylin nur in sehr spärlicher Masse auf.

Wenn wir nun dasjenige hervorheben, was sich bei allen 8 Kranken im *Marke des Grosshirns* findet, so ist in erster Linie eine *Gliawucherung in der Umgebung der Gefässe* zu verzeichnen. Diese *Gliawucherung hält sich jedoch nicht bloss an die infiltrierten, grösseren Hirngefässe, sondern tritt auch an den Capillaren und an solchen Blutgefässen auf, die noch keine Rundzelleninfiltration besitzen.* In allen Fällen sind die grösseren Hirngefässe mit *Lymphocyten infiltriert.*

KLEINHIRN.

Wie nach den portugiesischen Rapports die makroskopischen Leichenveränderungen an den Hirnhäuten in der Nähe und am Kleinhirne selbst am ausgeprägtesten sind, ebenso kann auch von den mikroskopischen krankhaften Gliaveränderungen des Kleinhirns dasselbe bestätigt werden. Es wird auch hier wiederum zuerst die graue Rindenschicht, dann die Schichte der Ganglienzellenkörner und endlich das Mark des Kleinhirns durchgenommen werden.

Nach den Bildern, welche meine Gliafärbung gibt, besteht ein ganz sonderbares Missverhältnis der Gliaveränderungen in der grauen Rinde des Kleinhirns und der oberflächlichen Granularschichte des Grosshirns. Während bei letzterem allenthalben zumal am oberflächlichsten Rande eine reichliche Gliavermehrung mit protoplasmatischer und Weigertscher Faserbildung sich feststellen lässt, zeigt beim Kleinhirn die graue Rinde eine nur ganz unbedeutende Gliawucherung. Ob das sich tatsächlich so verhält oder ob nicht vielleicht doch ein Fehler in der Methode vorliegt, vermag ich derzeit nicht zu entscheiden. Wenn wiederum Msubica als Beispiel zur Beschreibung genommen wird, so ist davon zu sagen, dass sich in der grauen Rinde des Kleinhirns grosse Felder finden, in welchen eine Zunahme der Glia kaum nachgewiesen werden kann; es sind die

Gliazellen kaum vermehrt und die Bergmannschen Fasern nur ganz unansehnlich verdickt. Dagegen gibt es aber andere Stellen, an welchen eine beträchtliche Wucherung

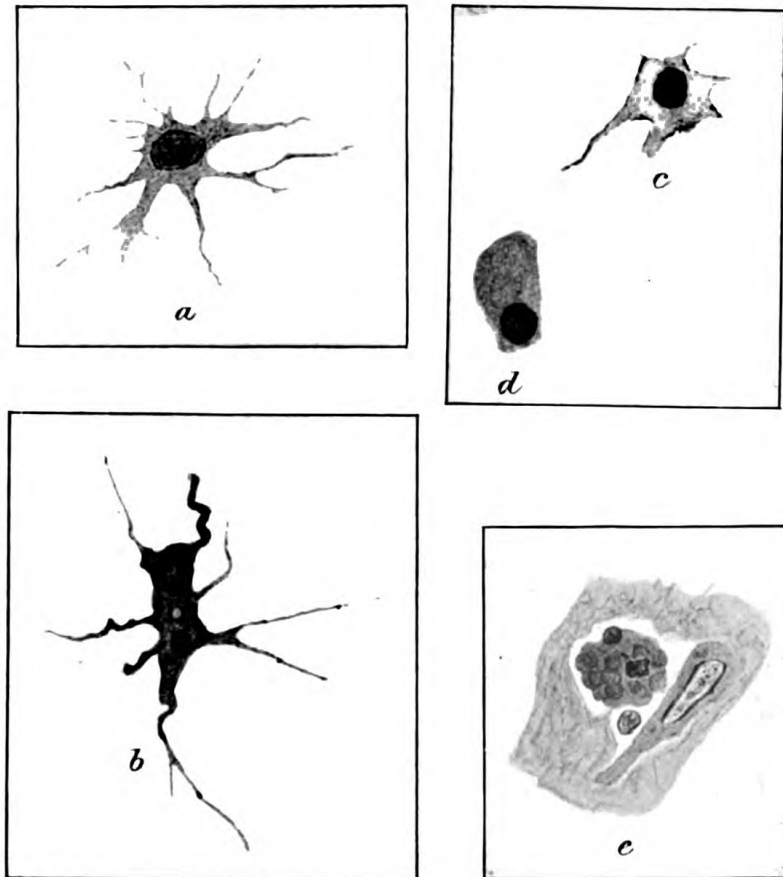


FIG. 5.

(a) Normale Gliazelle mit protoplasmatischen Zellfasern. (b) Gliazelle aus dem Marke des Grosshirns mit spiralig gedrehten und meanderlineanartig gewunden, protoplasmatischen Zellfortsätzen. (c) Gliazelle aus der oberflächlichen Granularschicht, hell rot gefärbt, zeigt nur mehr stummelige, kümmerliche Ausläufer. (d) Gliazelle ebenfalls aus der oberflächlichen Granularzone, leuchtend rot ohne Fasern. (e) Gliabegleitzelle aus der grauen Substanz des Rückenmarks, hochrot, von kugelter Gestalt und gebuckelter Oberfläche.

der Zellen mit meist schmalen, langgestreckten, in radiärer Richtung gelagerten Gliazellkörpern sich vorfindet. An diesen Zellen ist weniger die Vermehrung der protoplasmatischen Zellausläufer als vielmehr die Bildung von Weigert-

schen Gliafasern wahrzunehmen, welche in ganz auffälliger Weise vermehrt und verdickt sind. Die übrigen Fälle weisen das gleiche Verhalten auf. Infiltrierte Gefässe und Schollen sind nicht zu beobachten.

Im Allgemeinen kann also gesagt werden, dass in der *grauen Rinde des Kleinhirns eine Vermehrung der Gliaelemente wenigstens stellenweise festgestellt werden kann.*

Die *Körnerschichte* des Kleinhirns zeigt indes schon viel schwerere Veränderungen. Während hier in der Norm nur sehr schwer und sehr spärlich Gliafäserchen beobachtet werden können, finden sich bei Negrolethargie grosse, gemästete, mit dicken Fortsätzen versehene, zwischen die runden Nervenzellen eingelagerte Gliazellen. Diese haben grosse Ähnlichkeit mit Bild 5 b, sind aber viel üppiger und grösser und wohlgenährter. Hier finden sich neben solch progressiv veränderten Gliazellen auch solche in Rückbildung u. zw. in körnigem Zerfalle. Homogene Schollen sind vielfach festzustellen. Die verschiedenen Kranken zeigen in dieser Schichte nur geringe Verschiedenheit des mikroskopischen Bildes voneinander.

Alle Fälle zeigen eine sehr bedeutende Hyperplasie und Hypertrophie des Gliagewebes in der Körnerschicht des Kleinhirns.

Im *Marke* des Kleinhirns treffen wir wohl unter allen bisher betrachteten Gebieten die schwersten Veränderungen, die jedoch gegenüber den Beobachtungen im *Marke* des Grosshirns ausser dem graduellen Fortschritt keine neuen Erscheinungen bieten. Msubica besitzt mächtig gewucherte, dickleibige und vermehrte Gliazellen. Sowohl die runden Gliazellen als auch die, welche mit Fortsätzen versehen sind, weisen eine hochgradige Vermehrung auf und liegen namentlich in der Nachbarschaft der Gefässe dicht anein-dergelagert. Besonders zu bemerken ist, dass im *Marke* des Kleinhirns die Riesengliazellen nicht nur protoplasmatische Fortsätze gebildet haben, sondern auch Weigertsche Gliafasern in viel stärkerem Masse besitzen als im Grosshirn. Es finden sich auch reichliche Schollen. Die grösseren und mittleren Gefässe sind mit Lymphocyteninfiltrat und mit Gliawall umgeben, wie im Grosshirn. Auch hier ist zu

betonen, dass die Lymphocyten durch den Gliawall hindurch nicht in das Parenchym auszuwandern vermögen.

Die übrigen Fälle zeigen im Marke ein nur wenig vom Beschriebenen abweichendes, fast gleiches histologisches Verhalten. Selbst Kerongo zeigt hier einen übereinstimmenden Befund. Es finden sich gegenüber den Beobachtungen im Grosshirn nicht nur Zellen mit protoplasmatischen Ausläufern, sondern sogar mit Weigertschen Fasern. Gerade dieser Umstand macht das Verhalten der Glia in den Ganglienzellenschichten der Grosshirnrinde dieses Falles so unverständlich. Im Marke des Kleinhirns ist nämlich die Krankheit am weitesten vorgeschritten und hier finden sich nicht bloss deutliche protoplasmatische Fortsätze der Gliazellen, sondern sogar Weigertsche Fasern. Zu den Ganglienzellenschichten des Grosshirns verbreitet sich aber der Krankheitsprocess in der Negrolethargie nach den bisherigen Befunden an den Nervenzellen, an den Gefässen sowie auch an der Glia selbst am spätesten, und doch haben die Gliazellen, welche in der normalen Rinde deutliche Fortsätze tragen, diese in den Rindenschichten Kerongo's verloren, d. h. die Fortsätze sind unsichtbar geworden, ehe noch bemerkbare progressive Erscheinungen eingetreten sind. Diese Tatsache erregt den Verdacht, dass das Unsichtbarwerden der Gliazellausläufer möglicher Weise der hypertrophischen Wucherung vorausgeht. Ein anderer Grund, der mich in diesem Verdachte bestärkt, ist darin gelegen, dass die Gliazellkerne in der Rinde Kerongo's keine besonderen regressiven Veränderungen aufweisen, während im Marke des Kleinhirns zum mindesten ebenso schwere, wenn nicht schwerere, regressive Kernveränderungen der Glia vorfindlich sind, als im Marke des Grosshirns oben mitgeteilt wurden. Es sei hier nur die Tatsache von diesem sehr auffälligen Verhalten der Glia hervorgehoben. Bestimmtes hierüber werden uns erst weitere, gründlichere Erfahrungen lehren. Auch mehrere homogene Gliazellen, wie solche im Marke des Grosshirns bei Kerongo beschrieben wurden, mit verwaschenen Zellumrissen und kaum sichtbaren Ausläufern sind festzustellen. Einzelne kugelige Schollen sind auch zu beobachten nebst Lymphocyteninfiltration der grösseren Gefässe.

Allen Fällen eigen ist im Marke des Kleinhirns die überaus mächtige Wucherung der Glia und die Infiltration der grösseren und mittleren Blutgefässe mit Lymphocyten.

RÜCKENMARK.

Die Negrolethargie ist nicht eine Krankheit, welche auf bestimmte Gebiete des Centralnervensystems beschränkt bleibt, sie breitet sich überall hin aus und verschont keine Stelle. Das ist wohl leicht zu verstehen, wenn man bedenkt, dass die Krankheit mit dem Lymphgefässsystem in engstem Zusammenhange steht und von den allenthalben entzün-

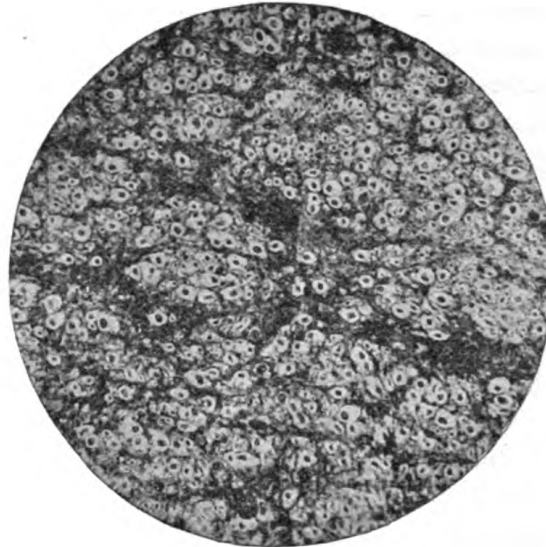


FIG. 4.

deten Meningen her ins Centralnervensystem einwandert. Im Rückenmarke werden alle Bündel und Stränge, die weisse wie die graue Substanz, kurz alle Gebiete ganz unregelmässig ergriffen. *Es kann daher nicht von System- oder Strangerkrankungen die Rede sein.* Am auffälligsten erkranken die Eintrittsstellen der hinteren Wurzeln, in deren Umgebung die Gliavermehrung am dichtesten auftritt. Wenn man nach den Segmenten des Rückenmarkes eine Einteilung vornehmen wollte, so schiene das in soferne

berechtigt, als die Krankheit im verlängerten Marke und oberstem Halsmarke vielleicht früher und, wenn die mehrfach beschriebenen Veränderungen an den Meningen einen Rückschluss auf das Mass der Erkrankung im Rückenmarke selbst zulassen, auch in etwas stärkerem Masse zu beobachten ist; aber auch hier finden so allmähliche Uebergänge statt, dass eine durchgreifende Einteilung nach den Segmenten, wenigstens in den von mir beobachteten Fällen, durchaus nicht zulässig ist. Falls man überhaupt eine Einteilung machen kann, so ist es vorderhand nur, dass die weisse und graue Substanz auseinander gehalten werden können. Es liegt jedoch ein Teil des *verlängerten Markes* von Msubica u. zw. aus der Gegend der Rautengrube zu Gebote. Hier treffen wir sehr schwere Veränderungen mit sehr vermehrten, dickleibigen Gliazellen, welche ein ganz homogenes glasiges Aussehen bieten, die Zellgrenzen nur sehr undeutlich erkennen lassen und nur eine Art Stummeln als Fortsätze tragen. Die Zellen sind auch wiederum in der Umgebung der Gefässe angehäuft. Dabei finden sich die mehrfach erwähnten Schollen in solcher Grösse und Zahl vor, wie sonst nirgends. Es ist ein ziemlich grosses Gefäss zu beobachten, welches eine ausgedehnte Infiltration von Lymphocyten und Wucherung der Glia zeigt. Dieser Befund kann auch an einem Schnitt aus dem untersten Teile des verlängerten Markes von Sempagana gesehen werden, wo an der Grenze der Pyramidenbahn (am Septum) ein mächtig infiltriertes Gefäss durch die weisse Substanz zieht; in weiter Umgebung ist die Glia in üppiger Wucherung. Die Achsencylinder sind zu Gruppen aneinander gedrängt durch vermehrtes und gewuchertes Gliagewebe und die Gliahüllen der Achsencylinder sind um das Vielfache verdickt.

An der *weissen Substanz des Rückenmarkes* von Msubica kann auf den ersten Blicke eine sehr erhebliche Vermehrung der Glia beobachtet werden. Die Gliazellkerne bieten ein verschiedenes Verhalten. Sehr viele sind normal, viele jedoch vergrössert, wie geschwellt und sehr hell gefärbt. Manche sind gekerbt oder gar gelappt, andere dunkel gefärbt und wie in Schrumpfung begriffen. Die Leiber der Glia-

zellen erscheinen beträchtlich grösser als gewöhnlich. Manche besitzen deutliche Zellgrenzen, während bei anderen das nicht der Fall ist. Eine grosse Zahl von Gliazellen bietet ein homogenes Aussehen und färbt sich mit Haematoxylin nur matt bläulich. Mehrere grossgewucherte Zellen befinden sich in körnigem Zerfalle. Abgesehen davon, dass die natürlichen Septa, die sich zwischen die einzelnen Rückenmarkstränge einschieben und diese abgrenzen, eine etwa 3—4 fache Verdickung erfahren, sind auch die Gliahüllen der Markscheiden, wie Bild 4 zeigt, wesentlich verdickt. Diese Verdickung ist nicht eine gleichmässige, oder symmetrische, sondern eine ganz unregelmässige. Am ausgeprägtesten ist sie an den Eintrittsstellen der Hinterstränge, an den Lissauerschen Feldern. Einzelne Markfasern sind wie Inseln voneinander abgesprengt in dicke Glia-scheiden eingebettet. Fast alle Markfasern sind jedoch noch erhalten und man findet nur sehr selten ein Lumen leer oder mit einer gequollenen Masse erfüllt. Es sind nicht viele Blutgefässe mit Lymphocyteninfiltration in der weissen Substanz des Rückenmarkes wahrzunehmen. Dagegen finden sich mehrere kugelige Schollen (Körnchenzellen).

Im Allgemeinen sind die Befunde in den übrigen fünf Fällen dem beschriebenen ähnlich. Auch hier soll gleich wie beim Grosshirn eine besondere Aufmerksamkeit der Lymphocyteninfiltration geschenkt werden, denn die Auffassung und Deutung des histopathologischen Processes hängt nicht zum Geringsten vom Verhalten der Rundzellen ab. Um das zu betrachten, wurde ein Gefäss mit seiner Umgebung (Fall Arcade) in Bild 3 dargestellt. Das Gefäss läuft an der Oberfläche des Rückenmarkes, hat eine sehr verdickte Wand und ist dicht umgeben von Lymphocyten (lz.). Allein auch hier ist zu beobachten, dass diese sich nicht durch den Gliawall (glw.) hindurch zu drängen und in das Parenchym einzuwandern vermögen. Denn es ist unschwer festzustellen, dass hart am Gefässe sehr viele aus dem Blute stammende runde Zellen sich befinden. Dass diese aber durch den Gliawall hindurch gelangen und sich wie früher behauptet wurde, im Parenchym einnisten,

kann nicht bestätigt werden, weil wir vom Gliawall aus gegen das Parenchym hin nichts finden als Axencylinder (axz.) und verdickte Gliahüllen mit vermehrten und vergrösserten Gliazellen.

Auch Kerongo zeigt hier im Ganzen und Grossen ein übereinstimmendes Verhalten, nur tragen auch im Rückenmark die Gliazellen zum grossen Teile jene besonderen Eigenschaften, die im Gross- und Kleinhirn beschrieben worden sind: dunkelgefärbter, geschrumpfter Kern, homogener, glasiger Zellkörper mit undeutlichen, schwer erkennbaren Zellumrissen und Zellfortsätzen. Bei Sempagana kann als eine bemerkenswerte Erscheinung hervorgehoben werden, dass am untersten Halsmarke die Gollischen Stränge eine vollkommen symmetrische Verdichtung des Glianetzwerkes besitzen, welche Verdichtung die Gliavermehrung in den übrigen weissen Teilen um etwas wenig übertrifft. Die symmetrische Verdichtung der Gollischen Stränge verliert sich nach abwärts allmählich und im mittleren Brustmarke ist nur mehr am linken Gollischen Strange eine asymmetrische vermehrte Gliagewebsvermehrung erkennbar. Weiter nach abwärts kann das Verhalten der Glia wegen mangelnden Materials nicht verfolgt werden.

Auch in der weissen Substanz des Rückenmarkes handelt es sich bei der Schlafkrankheit um eine Hyperplasie und Hypertrophie der Neuroglia.

GRAUE SUBSTANZ DES RÜCKENMARKES.

In der grauen Substanz sind die Gliaelemente in allen Fällen vergrössert und vermehrt. Es ist nicht leicht, die Glia, welche hier wie bei allen übrigen von mir untersuchten Fällen von Schlafkrankheit verwaschene Umrisse der Zellen aufweist, genauer zu beobachten. So viel ist jedoch sicher, dass die Zellkerne ebenso wie das Zellprotoplasma ein ähnliches Verhalten zeigen wie in den übrigen Gebieten. Die Wucherung der Glia ist mehr protoplasmatischer Natur, während die Weigertsche Faserbildung zurücktritt. Auch die übrigen Eigentümlichkeiten, die bei der Glia beobachtet wurden, wie die Undeutlichkeit der Zellfortsätze, das homo-

gene, glasige Aussehen einzelner Zellen (zumal bei Msubica und Kerongo) u. drgl. sind hier gleich wie in der weissen Substanz und wie im Gehirne vorhanden. Die Wucherung erstreckt sich in alle Gebiete und die Vermehrung der Glia ist am dichtesten und auffälligsten in der Umgebung der Gefässe. Worin sich die histologischen Veränderungen am meisten von jenen in der weissen Substanz unterscheiden, das ist die Infiltration der Gefässe. Während in der weissen Substanz, abgesehen von den verschiedenen Septen, infiltrierte Gefässe kaum bemerkt werden, befinden sich in der grauen besonders bei Msubica viele der grösseren und mittleren Gefässe infiltriert von reichlichen Lymphocyten, die, soviel wahrgenommen werden kann, das Verhalten zeigen, wie oben dargelegt wurde. Auch hier treten die Lymphocyten nicht durch den Gliawall hindurch und wandern nicht in das Parenchym aus, sondern bleiben auf die perivascularären Lymphräume beschränkt. Erwähnenswert ist ferner auch, dass in der grauen Substanz reichlicher als in der weissen, Schollen oben beschriebener Art zu sehen sind. Die übrigen 5 Fälle bieten geringere histopathologische Veränderungen als Msubica aber keine nennenswerten Abweichungen.

In allen Fällen ist die Vermehrung der Glia in der grauen Substanz des Rückenmarkes und die Infiltration der grösseren Gefässe mit Lymphocyten festzustellen.

Was nach den gemachten Wahrnehmungen den Grad der Erkrankung anlangt, ist zu bemerken, dass im Rückenmarke die obersten Gebiete vielleicht etwas stärker erkranken als die unteren. Die Ausdehnung der Gliawucherung auf Querschnitten erfolgt transversal, sie ist durchaus nicht gleichmässig sondern ganz unregelmässig, da mehr, dort weniger ausgebreitet.

Über die Ausbreitung des Processes im Grosshirn längs der Oberfläche und in die Tiefe kann wegen mangelnden Materiales nichts Genaueres ermittelt werden. Es ist jedoch die Annahme gerechtfertigt, dass bei der allgemeinen Erkrankung der Meningen auch die Rinde allenthalben die histopathologischen Erscheinungen bieten wird und dass der Process, der sich an die Gefässe hält, der Tiefe nach überall dort hin sich ausdehnt, wo grössere Blutgefässe verlaufen.

HYALINENTARTUNG.

Es finden sich, wie bereits erwähnt, im Gewebe des Centralnervensystems zerstreut mehrfach *schollenartige, rundlich, höckerige Gebilde*, welche das Mallorysche Haematoxylin nicht annehmen, sondern bläulich weissgrau bleiben. Sie lösen sich auch nicht in der von mir angewendeten Gerb- und Pikrinsäure. Diese Körperchen wurden bereits von Mott beobachtet und als „granule Cells“ beschrieben. Sie liegen teils in der Nachbarschaft der Gefässe, teils an solchen Stellen, wo von einem Gefässe nichts zu sehen ist. Die einen davon sind kugelig mit glatter Oberfläche, die anderen sind oberflächlich etwa wie eine Himbeere mit Buckeln versehen. Vielfach liegt in diesen kugeligen Gebilden noch ein dunkel gefärbter, geschrumpfter Zellkern.¹ Schon diese Befunde veranlassen mich, weiter zu ermitteln, woraus die besagten scholligen Bestandteile und Gefässverdickungen bestehen. Aber eine andere Wahrnehmung gab noch mehr Anlass zu weiteren Untersuchungen; im Falle Kerongo nämlich fanden sich, wie erwähnt, ganz eigentümlich veränderte Gliazellen, die ein glasig homogenes Aussehen besitzen, wenig Haematoxylinfarbe aufnehmen, sehr undeutliche Umrisse zeigen und deren Fortsätze kaum wahrgenommen werden können. Dieses auffällige Verhalten der Gliazellen erweckte den Verdacht, ob hier nicht etwa irgend eine Entartungsform vorliegt, welcher homogenes Aussehen der Masse eigen ist. Es lag sehr nahe, daran zu denken, dass es sich vielleicht um Amyloid—oder Colloid—oder *Hyalinentartung* handeln könnte.

Die Versuche auf Amyloid ergeben aber sowohl mit der Iod—als auch mit der Methylviolettreaction kein positives Ergebnis. Wohl aber zeigen in den nach van Gieson behandelten Schnitten sowohl die erwähnten Schollen, als auch die verdickten Gefässwände und einzelne der homogen entarteten Gliazellen eine hell leuchtend rote Farbe. Es handelt sich jetzt um den Nachweis, ob man es hier mit

¹ Einzelne Gefässwände sind wie durch eine ein- oder angelagerte homogene Masse verdickt.

Hyalin oder Colloid zu tun hat. Nachdem hierüber die Pathologen,² noch keine eindeutigen Ansichten besitzen, sei hier zur Vermeidung von Missverständnissen angeführt, dass ich mich bei Entscheidung dieser Frage an die Grundsätze halte, welche Alzheimer für seine diesbezügliche Arbeit massgebend waren. Ich bin um so mehr genötigt, das zu tun, weil es mir in der kurzen, verfügbaren Zeit nicht möglich ist, die ganze weitere Literatur zu sammeln und weil die in der Fachliteratur in den letzten Jahren veröffentlichten einschlägigen Abhandlungen von Evensen und Dercum, wovon ersterer über hyaline, letzterer über colloide Entartung der Hirngefässe berichtet, keine besseren Anhaltspunkte zur Schlichtung der Frage bringen. Da mir die Zeit nicht langt, alle 8 oben behandelten Fälle auch nach dieser Richtung hin genau zu bearbeiten, muss ich mich mit 3 zufrieden stellen. Diese betreffen Kerongo, Msubica und Sempagana.

Bei Kerongo zeigen sich in der Färbung mit van Gieson zwar nur wenige Gefässwände des Hirn und Rückenmarkes mit hochroten homogenen Ringen oder im Längsschnitt mit schmalen homogenen gleichfalls leuchtend roten Leisten eingelegt. An manchen Stellen liegen neben den Gefässen spärliche gleichartige Schollen vom Umfange einer grossen runden Gliazelle. Ausserdem sind hier mehrere u. zw. gerade immer jene oben beschriebenen Gliazellen, welche schon bei der Gliafärbung dunkeln Kern, homogenes Aussehen und verwaschene Umrisslinien zeigen, in verschiedenen abgestuften Farbtönen hellrot gefärbt und heben sich gegenüber den anderen blassrot aussehenden Gliazellen deutlich ab. Auch die Pyramidenganglienzellen weisen eine Färbung auf, die ganz auffällig hochrot ist, wenn auch eine homogene Veränderung sich an denselben nicht feststellen lässt. Bei der Färbung Msubica finden sich auch einzelne Gliazellen, welche sehr grossen homogenen Körper besitzen und auffällig hellrot gefärbt sind. Es liegen aber zahlreiche kugelige homogene Schollen von der Grösse einer

² Wie Ziegler in der letzten Auflage seiner Allgemeinen Pathologie und pathologischen Anatomie ausführt.

grossen runden Gliazelle und von hell leuchtend roter Färbung zerstreut im ganzen Centralnervensystem herum, sowohl im Grosshirn wie namentlich in der Körnerschichte und im Marke des Kleinhirns, im verlängerten Marke und im Rückenmarke sind solche Kugeln zu beobachten. Aus der grauen Substanz des Rückenmarke stammt die buckelige Scholle (fig. 5 d), welche in einem pericellulären Raume neben einer Neurogliazelle liegt und einen noch sichtbaren dunkeln Kern besitzt. Wegen dieses Zellkernes und, weil ein Gefäss mit Bindegewebe in der Nähe nicht zu finden ist, bin ich gedrungen, anzunehmen, dass es sich um eine hyalin entartete Gliazelle handelt. Die Gefässe zeigen keine deutlichen hyalinen Veränderungen und die Nervenzellen sind von gewöhnlichem Farbenton. Im letzten Falle, Senipagana, treffen wir hellrot gefärbte Kugeln von obiger Beschaffenheit im Grosshirn und Rückenmark. In letzterem sind auch Gefässe zu beobachten, welche denjenigen des ersten Falles gleich sind.

Um also die Entscheidung, zu fällen, ob es sich bei den beschriebenen pathologischen Gewebsveränderungen um Hyalin oder Colloid handelt, wurden verschiedene mikrochemische Proben gemacht. Der zur Celloidineinbettung einzelner Stücke angewandte Alkohol brachte die Schollen nicht zur Lösung und die in meiner Färbung angewandte Gerb- und Pikrinsäure führten auch keine Auflösung herbei. Desgleichen wurden die Schollen weder durch kochen in Wasser, noch auf Zusatz von Kaliumhydroxydat zur Schwellung gebracht oder gelöst. Alle nach dieser Vorbehandlung nach van Gieson gefärbten Schnitte weisen die gleichen Bilder auf, wie die direct so gefärbten. Das Eosin färbt die besagten Bestandteile glänzend, hellrot, ähnlich wie das Säurefuchsin (van Gieson), während hingegen durch das Karmin eine Färbung nicht erfolgt. Eine Probe mit Weigerts Fibrinmethode wurde deshalb nicht gemacht, weil in Alkohol gehärtetes Materials von diesen Fällen nicht zur Verfügung stand. Nach den Ergebnissen obiger Proben werden wir die *vorliegende Art der Gewebsveränderung wohl als eine solche aufzufassen haben, welche der Hyalinentartung am nächsten steht.*

Das Bedeutsame an diesen Befunden liegt nicht so sehr in der hyalinen Entartung der Gefässe, die ja schon öfter beschrieben worden ist, sondern vielmehr in der Bestätigung dessen, was in der mir zugänglichen Literatur bisher nur Kromayer beobachtete, und das ist die *hyaline Entartung der Neuroglia*. Meine Wahrnehmungen drängen mich, diese Behauptung Kromayer's zu bestätigen u. zw. deshalb, weil ich alle Uebergangsformen von der schwer krankhaft veränderten, homogen aussehenden Gliazelle bis zur untrüglichen, hell leuchtend rot gefärbten Hyalinscholle zu beobachten in der Lage bin. Es gibt nämlich Gliazellen, welche zwar homogen glasig aussehen, aber das Säurefuchsin der van Giesonschen Färbung kaum in beträchtlicheren Masse aufnehmen als die normalen Gliazellen. Dann finden sich solche, welche die Zellausläufer nur mehr mangelhaft erkennen lassen und schon sehr auffällig hellrot gefärbt sind (Fig. 5, c). Weiter stellt Fig. 5, d, eine Gliazelle dar, die schon kugelig ist, vollends verwaschene Grenzlinien besitzt und bereits leuchtend rot aussieht (beide aus der oberflächlichen Granularschicht der Grosshirnrinde) und endlich finden wir (Fig. 5, e) die vollendetete Hyalinscholle, welche in einem pericellulären Raum liegt und nicht anders aufgefasst werden kann, als eine degenerierte Gliabegleitzelle.

Über das Auftreten der Hyalinentartung bei Negrolethargie wird man sich nicht wundern, wenn man in Erwägung zieht dass hiebei das Gewebe einer sehr chronischen, langsamen Inanition und einem beträchtlich gesteigerten, unausgesetzten intracraniodorsalen Druck ausgesetzt ist, welcher letzterer Umstand auch in den Beobachtungen von Holschewnikoff, Liebmann und Alzheimer zutraf und der ja auch die Ernährung schwer beeinträchtigen hilft.

An den übrigen 5 Fällen konnte ich nicht mehr, wie bei den 3 beschriebenen, die sehr vielfältigen und zeitraubenden Proben auf Hyalin vornehmen. Allein glasige Schollen wurden noch an weiteren 4 Fällen schon mit der Gliafärbung vorgefunden bei Wasiwa, Arcade, Nonbi und Goavera und verdickte auf Hyalin verdächtige Gefässwände waren bei Hamesi und Nonbi zu sehen. Daraus ergibt sich vorderhand zwar nicht die Behauptung, wohl aber die sehr be-

gründete Vermutung, dass die hyaline Entartung bei der Negrolethargie eine sehr häufige, vielleicht ständige Erscheinung ist; selbstverständlich, wenn es sich um chronische, vorgeschrittene Fälle handelt. Genaueres hierüber müssen erst weitere *Untersuchung feststellen*.

Kurz zusammengefasst bestehen die Endergebnisse der vorliegenden Untersuchungen darin, *dass man bei der Schlafkrankheit im Gehirn und Rückenmark eine Stauung der Lymphe von den Meningen her, welche eine massenhafte Infiltration mit Lymphocyten aufweisen, wahrnimmt. Die Stauung rückt längs der Lymphstränge, welche die grossen Gefässe begleiten, gegen die kleineren vor und breitet sich sowohl von der Oberfläche des Gehirns als auch vom Marke her gegen die Rinde hin aus. Neben dieser Lymphstauung findet aber auch immer eine üppige Wucherung der Neuroglia statt, eine Wucherung, die gleich wie die Lymphstauung einerseits von der oberflächlichen Rindenzone, andererseits längs der Blut- und Lymphgefässe vom Marke gegen die Rinde vorwandert, jedoch aber der Lymphstauung vorausgeht.*¹ Dabei bleibt das Parenchym sowohl in den Ganglienzellen als auch in den Achsencylindern am längsten gesund und wird überhaupt am wenigsten von der Krankheit geschädigt.

Nach diesen Ermittlungen, welche für das Verständnis und die Deutung des Krankheitsprocesses von grundlegender Wichtigkeit sind, fragt es sich, ob die bisherige Meinung der Autoren, welche die Krankheit für eine *Meningo-Encephalo-Myelitis* hielten, noch zurechtbestehen kann? Alle bisherigen Histologen lenkten ihr Augenmerk besonders auf die Blutgefässe und die Ganglienzellen und arbeiteten mit solchen Färbemethoden (z. B. Nissl's und Unna's Nervenzellenfärbungen), in welchen neben den Zelleibern der Nervenzellen wohl die Kerne der übrigen Zellen, nicht aber deren Zellkörper mit hinlänglicher Deut-

¹ Regressive Veränderungen sind allerdings auch aber in verhältnismässig sehr spärlicher Masse vorfindlich und bestehen teils in atrophischer Schrumpfung der Gliazellen, teils in körnigem Zerfall, wie ihn Alzheimer bei Paralyse beschrieb, und teils in hyaliner Entartung derselben.

lichkeit gefärbt werden. Dabei beobachteten sie wohl die in vorgerücktem Stadium der Negrolethargie in Massen vorhandenen Lymphocyten mit einigen Plasmazellen. Ueber den Leib der Gliazellen hingegen blieben die Forscher unaufgeklärt, weil sie eben keine entsprechende Färbemethode anwandten, welche den Gliazellleib deutlich genug zur Darstellung bringt, und vermochten daher nicht, die runden Gliazellen von den ebenfalls runden Blutelementen scharf auseinander zu halten. Zwar hat Nissl schon vor längerer Zeit darauf aufmerksam gemacht, dass mit seiner Färbung auch die Gliazellleiber, besser als mit der Weigertschen electiven Gliafärbung wahrgenommen werden können, und darauf hingewiesen, dass vieles was Glia ist, in fälschlicher Weise für mononucleäre Leukocyteninfiltration angesehen wird. So war es auch hier geschehen. Alle Histopathologen der Negrolethargie berichteten in auffälliger Übereinstimmung über ausgedehnte Zellinfiltrate in den Lymphscheiden der Blutgefäße, über Leukocytenwanderung in das Parenchym und Stützgewebe des Centralnervensystems und erklärten sich diese Befunde damit, dass sie der Krankheit eine entzündliche Ursache zugrunde legten.

Meine Beobachtungen weichen nun aber gänzlich von jenen der bisherigen Histologen ab. Während diese meine Abhandlungen, teilte Mott im November 1906 in dem Seventh Report of the Sleeping Sickness Commission of the Royal Society die Wahrnehmungen mit, welche er mit der Polychrom Eosin—und mit Heidenhains Haematoxylin—Eosinfärbung an der Glia bei Erkrankungen der Centralnervensystems nach Trypanosomeninfectionen gemacht hatte. Diese Befund zeigen einige Ähnlichkeit mit meinen Beobachtungen an der Glia bei Negrolethargie. Dass meine Befunde von jenen der vorausgegangenen Beobachter verschieben ausfielen, das musste wohl so kommen, denn ich untersuchte nicht mehr mit einer Färbemethode, welche, abgesehen von den Nervenzellen, die übrigen epidermalen und mesodermalen Gewebe des Centralnervensystems nur im Kerne färbt, sondern ich benützte eben eine Färbung, welche den Leib der Gliazelle ersichtlich macht und so die Möglichkeit gewährt, die Neurogliazelle

von anderen Zellen mit rundem oder überhaupt gliaähnlichem Kern auseinander zu halten. Da habe ich nun gefunden, dass wohl in den perivascularären Lymphräumen namentlich in vorgeschrittenen und chronischen Fällen ausgedehnte Lymphocyteninfiltrate sich finden. Ich fahndete viel und in allen Fällen nach Lymphocyten auch in der Rinde und im Marke des Gehirns, sowie im Rückenmarke, allein unter allen Zellen, deren Identität ich festzustellen imstande war, konnte ich weiter abseits von den Gefässen nie Zellen bemerken, die ich als vom Blute her stammend bezeichnen könnte. Es ist vielmehr wahrzunehmen, dass um die infiltrierten Lymphscheiden herum sich ein förmlicher Gliawall bildet. Innerhalb dieser Gliabmarkungszone, d. i. gegen das Gefäss hin und manchmal auch im Geflechte der Abmarkungszone selbst kann man Bestandteile, die dem Blute zugehören, finden, aber über den Gliawall hinaus gegen das Nervengewebe hin, ist es nicht gelungen, andere Zellen mit rundlichem Zellkern als nur Gliazellen zu entdecken. Die Behauptung, *dass auch Mark und Rinde und die pericellulären Räume der Nervenzellen bei der Negrolethargie von ausgewanderten Leukocyten eingenommen sind, kann nach diesen Darlegungen nicht mehr zurecht bestehen, denn die Leukocyteninfiltration bleibt lediglich auf die perivascularären Lymphräume beschränkt.*

Um die Frage, ob die Negrolethargie einen entzündlichen Process der Hirn-Rückenmarksubstanz darstellt, weiter zu verfolgen, ist es erforderlich, auszumitteln, woher die erwähnte Lymphocyteninfiltration kommt. Es könnte natürlich sehr leicht der Fall sein, dass es sich um entzündliche Infiltrate handelt. Zum mikroskopischen Bilde einer Entzündung gehört aber ein gesteigerter Blutzufuss zum entzündeten Organ mit Dehnung und Vermehrung der Blutgefässe und mit Austritt von Blutelementen in das umgebende Gewebe, sei es durch Rhexis, sei es durch Diapedesis. Zwar berichtet mir Mott mündlich, in seltenen Fällen Haemorrhagien gesehen zu haben, es gelang mir aber nicht, in den vorliegenden 8 Fällen, wovon mir leider nur je ein oder zwei kleine Stücke zur Verfügung standen, Blutungen entzündlicher oder anderer Herkunft zu finden.

Kein auffallend vermehrter Blutzudrang zum kranken Gewebe, keine Vermehrung der Gefässe und keine directe Auswanderung von Blutelementen aus den Blutgefässen konnten nachgewiesen werden. Es war auch nicht möglich, primäre Infiltrate an den Capillaren, wo ja bei der Entzündung immer sich die Zellanhäufung zuerst findet, festzustellen. Hingegen aber war in allen Fällen und allenthalben wahrzunehmen, dass die Leukocyteninfiltrate längs der Scheiden der grossen Gefässe einerseits von der Oberfläche des Gehirns, andererseits von dessen Marke her gegen die mittleren Rindenschichten, welche am längsten verschont bleiben, vorrücken. Ein derart entstandenes Rundzelleninfiltrat kann niemals als solches betrachtet werden, das durch einen entzündlichen Process an Ort und Stelle selbst erzeugt wurde, denn, wie bereits gesagt, da müsste die Infiltration an den Haargefässen beginnen. *Das Infiltrat*, welches bei der Negrolethargie beobachtet wird und welches zuerst *in der Umgebung der grossen Blutgefässe den Anfang nimmt, kann nur als eine Stauung der Lymphe* von aussen, von den Meningen her, *gedeutet werden*.

Ein anderer, sehr wichtiger Umstand ist der, dass es nie gelang in der Umgebung der erwähnten Infiltrate *entzündliche Necrose* des Gewebes nachzuweisen. Bei einem mit so massiger Infiltration einhergehenden, chronischen Process müsste man, wenn er entzündlicher Natur wäre, doch wenigstens an manchen Stellen eine Necrose finden, was indes *nie geschehen konnte*.

Um nun noch das Verhalten des *Nervenstützgewebes* im Besonderen in Betracht zu ziehen, sei dasjenige, was schon früher gesagt wurde, noch einmal kurz hervorgehoben. Die Glia befindet sich in üppiger Proliferation. Die Wucherung beginnt an der Rindenoberfläche, was bei den chronischen Veränderungen an den Hirnhäuten ja als etwas fast selbstverständliches erscheint. Diese oberflächliche Neuroglia-wucherung zieht aber nicht sehr tief in die Rinde herein, denn selbst in den vorgeschrittensten Fällen konnte die Gliavermehrung der Rindenoberfläche nie weiter verfolgt werden, als bis in die Gegend des Baillarge-Gennarischen Streifens. An der Oberfläche der Rinde erfolgt die Glia-

wucherung diffus und ist ähnlich wie bei der Paralyse an den Eintrittstellen der Gefässe mächtiger und dichter. Eine andere ebenfalls sehr mächtige und üppige Zunahme des Nervenstützgewebes vollzieht sich im Marke und zwar in der Umgebung der grösseren Hirngefässe, ist aber nicht erst hervorgerufen durch die Lymphocyteninfiltration, sondern wandert dieser stets voraus und findet sich an sehr vielen Stellen schon dort, wo von einer Lymphocytenanhäufung noch gar nichts zu sehen ist. Am Rückenmarke finden wir an der Oberfläche und in der Tiefe einen ganz gleichen Hergang und dasselbe Verhalten der Neuroglia. Dieses Verhalten des Nervenstützgewebes ist für die Frage, ob die Schlafkrankheit ein entzündlicher Vorgang ist, von massgebender Bedeutung. Bei einer Entzündung ist der Verlauf der, dass die Wucherung des Bindegewebes an Stelle des zugrunde gegangenen Parenchyms regenerierend einsetzt. Wir haben also bei der Entzündung zuerst Hyperaemie und Leucocyteninfiltration, dann Nekrose und nach dieser die Wucherung der Binde substanz, bei Negrolethargie hingegen treffen wir *zuerst starkes Wachstum der Neuroglia und hinterher kommt erst die Leukocyteninfiltration.*

Diese Erwägungen lehren uns 1., dass die Behauptung, das Nervengewebe, die Rinde wie das Mark seien bei Schlafkrankheit von ausgewanderten Lymphocyten besetzt, nicht mehr haltbar ist, und dass das Vorhandensein von Blut- und Lymph elementen auf die perivascularären Lymphräume beschränkt bleibt. 2. Dass die Einwanderung der massenhaften Lymphocyten nicht durch die Capillaren erfolgt, sondern auf dem Wege der Lymphbahnen längs der grossen Gefässe vor sich geht u. zw. durch Rückstauung der Lymphe. 3. Dass bei Negrolethargie nekrotische Umwandlungen des kranken Gewebes in den vorliegenden 8 Fällen nicht nachgewiesen werden konnten und endlich. 4. Dass die starke Wucherung des Stützgewebes der Lymphocyteninfiltration nicht nachfolgt, sondern vorausgeht. *Denmach wird auch die Behauptung hinfällig, die Schlafkrankheit stelle einen entzündlichen Process der Hirn- und Rückenmarksubstanz dar.*

Wenn nun die Negrolethargie entgegen den bisherigen Ansichten keine Entzündung darstellt, welchen pathologischen Vorgängen soll sie dann zugezählt werden? Es müssen hier zweierlei Dinge unterschieden werden, nämlich die Stauung der Lymphe und die Wucherung der Glia. Die Stauung der Lymphe erfolgt von den Meningen her und breitet sich längs der grossen Gefässe aus. Ob hier einfache Stauung vorliegt oder ob in den Lymphgefässen auch entzündliche Processe vor sich gehen, vermag ich heute weder zu behaupten, noch zu bestreiten, es wäre ja möglich, dass wir es mit einer allgemeinen Lymph-aden-angioitis zu tun haben, die aber, so weit sie im Gehirn und Rückenmark vorkommt, sicher nicht durch die beschriebenen Gliawälle hindurch auf das übrige Stützgewebe und das Parenchym des Gehirn-Rückenmarkes übergeht. Für die Auffassung des Processes, der sich in der Hirn-Rückenmarksubstanz abspielt, ist es ja nicht von wesentlichem Belange ob die Vorgänge an den Lymphbahnen lediglich Stauung oder aber Stauung mit Entzündung der Gefässe darstellen, denn ebenso wie eine Arteriosclerose der Gefässe allein noch keine Encephalitis oder Myelitis ausmacht, ebenso kann auch die Lymphangoitis noch keine Entzündung der Hirn-Rückenmarksubstanz sein. Während bei der Negrolethargie nach den Beobachtungen von Mott das Parenchym der Nervensubstanz verhältnissmässig lange gut erhalten bleibt, muss betreffs des Nervenstützgewebes hervorgehoben werden, dass es meistens mächtige Wucherungen zeigt. Nachdem für die Gliavermehrung eine entzündliche Ursache nicht angenommen werden kann, wird man in erster Linie an hypertrophische Wucherung zu denken haben, denn an multiple herdförmige Gliawucherung wie bei der multiplen Hirn-Rückenmarksclerose kann bei der gleichmässigen Gewebswucherung, durch welche die Hirngefässe der Schlafkranken gleichsam von einem Neurogliafilzwerke umspinnen werden, nicht gedacht werden. Den Charakter einer anderen gliösen Neubildung im engeren Sinne hat die Gliavermehrung in der Schlafkrankheit auch nicht, denn es fehlt vollends die örtliche Abgrenzung eines Tumors und die bei Gliomen so vielfach wahrgenommenen Erschei-

nungen regressiver Natur. Es bleibt daher nur übrig, eine ausgebreitete hypertrophisch - hyperplastische Gliawucherung anzunehmen, welche sich in erster Linie längs der Gefässe allenthalben ausbreitet und sich im Rückenmarke auch in das Gebiet der normalerweise vorhandenen Gliahüllen der Markscheiden erstreckt. Nach dem, was in den 8 untersuchten Gehirnen und in den 6 Rückenmarken sich vorfindet, handelt es sich bei der Negrolethargie 1. *um eine von den Meningen her sich ausbreitende Lymphocytenstauung in den perivascularischen Lymphräumen der Gefässe und 2. um eine Hypertrophie und Hyperplasie der Neuroglia, welche sich besonders in der Umgebung der Gefässe geltend machen.* Dabei wird der Säftekreislauf und die Ernährung unmöglich gemacht und es stellt sich am Ende eine Art *hyaliner Degeneration* der Gewebe ein.

Die *Erklärung der Lymphstauung* hält wohl nicht schwer, wenn man weiss, dass eine chronische allgemeine Lymphadenitis und, wie behauptet wird, auch eine chronische Meningitis cerebrospinalis vorliegen. Etwas schwieriger ist die *Erklärung der Wucherung des Stützgewebes*. Da wird wohl in erster Linie die entzündliche Lymphstauung verantwortlich gemacht werden müssen. Mit dieser Ursache allein finden wir aber schon darum nicht das Auskommen, weil an vielen Stellen Gliawucherung vorhanden ist, wo von einer Lymphstauung noch nichts zu sehen ist. Darum ist es nötig nach anderen Gründen zu suchen. Wenn man in Erwägung zieht, dass durch die Vermehrung der Cerebrospinalflüssigkeit und durch die Massenansammlung von Lymphocyten in den Meningen und in den Lymphräumen um alle grösseren Gefässe herum eine sehr erhebliche Steigerung des intracraniodorsalen Druckes, der bisher bei der Krankheit noch nicht gemessen worden ist, statthaben muss, kann man füglich nicht anders, als diese Drucksteigerung zum Wenigsten als wichtigen Nebengrund der Neurogliavermehrung anzusehen. Die Drucksteigerung in der Schädel- und Wirbelhöhle kann uns indes auch nicht eine erschöpfende Erklärung aller vorfindlichen Befunde bieten, denn es bleibt unerklärt, warum gewisse Stellen der Rinde z. B. der Kamm eines Gyrus, der dem Drucke

sicher viel stärker ausgesetzt ist als verschiedene Gebiete des Markes, von der Gliose (im Gebiete der Nervenzellschichten nämlich) erst ganz spät und im vorgerückten Stadium ergriffen wird, und weiter ist es auch nicht ganz einleuchtend, warum sich die Gliavermehrung gerade an die Verzweigung des Blutgefässsystems hält, auch dort, wo von einer wirklicher Lymphstauung und Lymphocyteninfiltration noch nichts zu beobachten ist. Nachdem es sich bei der Negrolethargie unzweideutig um Lymphstauung handelt, ist leicht einzusehen, dass infolge gehemmten Abflusses der Lymphe und ungenügenden Kreislaufes der Körpersäfte sich Giftstoffe, Toxine, zumal in den verlegten Lymphräumen ansammeln. Diese Toxine sind natürlich nicht an die Lymphocyteninfiltration gebunden, sondern dringen dieser voraus viel tiefer in die perivaskulären Lymphräume ein und können die der Rundzelleninfiltration weit vorausseilende perivaskuläre Gliawucherung verursachen. Wir werden also für die Wucherung des Nervenstützgewebes bei der Negrolethargie *die Lymphstauung, die Vermehrung des intracraniodorsalen Druckes* und das Vorhandensein von *Toxinen* vorläufig gemeinsam verantwortlich machen.

Und nun stehen wir vor der Frage, wie sich das mikroskopische Bild der Schlafkrankheit von dem anderer Erkrankungen des Centralnervensystems auseinanderhalten lässt. Bei dieser *Differenzialdiagnose* werden in erster Linie die progressive Paralyse, dieluetische Meningo-encephalitis und vielleicht noch die multiple, disseminierte Sclerose, sowie die arteriosclerotische Hirnerkrankung in Betracht kommen.

Wenn man die histologischen Veränderungen der Glia bei *progressiver Paralyse* nach den Darstellungen Alzheimers verfolgt, ist man wahrlich in der Lage sehr viele Ähnlichkeiten zwischen Negrolethargie und Paralyse herauszufinden. Alzheimer schreibt, „dass bei Paralyse regelmässig eine erhebliche Wucherung des Stützgewebes stattfindet, die Wucherung führt zur Bildung zahlreicherer und grösserer Gliazellen, welche eine Menge Fasern bilden und schliesslich in den vorgeschrittenen Fällen von Paralyse zur Bildung dichtfaseriger Geflechte in Rinde und Mark

Veranlassung geben. Der Hauptteil der neugewucherten Glia wird dazu verwendet, die oberflächlichen Glia-schichten zu verstärken. Besonders auffällig ist die Verstärkung der Glia-scheiden der Gefässe." Alles das, was über das Verhalten der Glia bei Paralyse in diesen Sätzen gesagt wird, kann fast wörtlich auch auf die Veränderungen bei Schlafkrankheit angewendet werden, und doch sind die histologischen Bilder so ganz voneinander verschieden. Schon das Bild der Gliazelle ist bei der Paralyse und Negrolethargie ein anderes. Während bei ersterer die vergrößerten Gliazellen scharf geschnittene Ränder und deutlich abgegrenzte, leicht sichtbare Fasern mit gewöhnlich reichlichem Weigertschen Faserstoff besitzen, sieht man an der charakteristischen Gliazelle bei Negrolethargie die Umrisse des mächtig vergrößerten Zelleibes nur undeutlich und die Ausläufer der Zellen sind, wenn man von jenen in der oberflächlichen Granularschichte absieht, nur protoplasmatischer Natur und besitzen verhältnismässig nur spärliche Weigertsche Fasern. Auch die Ränder der Fasern sind vielfach verwaschen und nur schwer zu sehen. Ein anderes Unterscheidungszeichen, das die Wucherung der Glia im Allgemeinen betrifft, ist darin gelegen, dass bei der Paralyse in der Markleiste eine durchziehende Schicht mächtig gewucherter Glia beobachtet werden kann, während bei der Schlafkrankheit in der radiären Zone nur stellenweise u. zw. immer nur in der Umgebung der Gefässe eine Gliavermehrung festzustellen ist. Ferner muss als weiterer Unterschied zwischen beiden Krankheiten die Bildung von Gliawällen um die infiltrierten Gefässe herum bei Negrolethargie angeführt werden. Zu diesen Kennzeichen kommen aber noch andere histologische Verschiedenheiten. Während bei Paralyse die grösseren und kleineren Gefässe infiltriert sind, finden wir bei Negrolethargie, dass mit besonderen Vorzuge gerade die grösseren und mittleren Blutgefässe zuerst Lymphocyten-Infiltration besitzen, während die kleinsten Gefässchen davon am längsten verschont bleiben. Schliesslich wäre noch zum Verhalten des Parenchyms zu erwähnen, dass dieses bei der Paralyse nach den bisherigen Mitteilungen zuerst erkrankt, während es bei Negrolethargie nach den

Beobachtungen von Mott lange verschont bleibt und überhaupt nicht in sehr schwerer Weise in Mitleidenschaft gezogen wird. Das geht wohl auch daraus hervor, weil bei der Negrolethargie der schichtenmässige Bau der Rinde erhalten bleibt, während er bei Paralyse verloren geht und weil man bei Schlafkrankheit die Achsencylinder in Marke des Gehirns und im Rückenmarke fast wie in der Norm vorfindet, während sie bei Paralyse zumal in der Marksubstanz des Grosshirns nur sehr spärlich, in manchen Fällen fast gar nicht mehr zu beobachten sind. Bei der Negrolethargie muss die Gliawucherung als der primäre Process aufgefasst werden, während sie bei der Paralyse erst secundär, nach vorausgegangenen Schädigungen des Parenchyms auftritt. Nach diesen Grundzügen ist die histologische Unterscheidung beider Krankheiten wohl nicht sehr schwer.

Eine andere Krankheit, bei welcher man gerade wegen der Miterkrankung der Meningen und wegen der Infiltration der Gefässe im ersten Augenblicke an Ähnlichkeit mit der Schlafkrankheit denken könnte, ist die *luetische Meningo-Encephalitis*, und das um so mehr, als man ja die Negrolethargie bis nun für einen entzündlichen Process ansah. Als wichtigstes differenzial diagnostisches Kennzeichen muss gleich angeführt werden, dass die luetische Meningo-encephalitis nach Alzheimer einen wirklichen entzündlichen Process darstellt, während nach den obigen Darlegungen das von der Negrolethargie nicht mehr behauptet werden kann. Die luetische Meningo-Encephalitis rückt von den Meningen her gegen die Rinde vor und zerstört diese. Bei der Schlafkrankheit zieht die Erkrankung sowohl von den Meningen als auch von den Gefässen des Marks her und lässt die Ganglienzellenschichten der Rinde am längsten verschont. Während sich bei der luetischen Meningo-Encephalitis die Gliawucherung an die entzündlichen Herde hält, breitet sie sich bei Negrolethargie immer längs der Gefässe hin aus, selbst dorthin, wo von einer Infiltration noch nichts zu sehen ist. Bei der Meningo-Encephalitis vermag sich die Glia gegenüber den einwandernden Rundzellen nicht zu halten und wird zum Teile von letzteren

zerstört, bei der Schlafkrankheit dagegen bilden sich die beschriebenen Gliawälle und behindern das Auswandern der Lymphocyten aus den perivascularären Lymphräumen in das Nervenparenchym. Es wird berichtet, dass bei Meningo-Encephalitis luetica die Infiltrate Neigung zu raschem Zerfalle haben, während bei der Negrolethargie Nekrosen in den acht untersuchten Fällen nicht beobachtet werden konnten. Nach alledem lassen sich die luetische Meningo-Encephalitis und die Negrolethargie mikroskopisch leicht als voneinander grundverschiedene Prozesse auseinander halten.

Von¹ anderen Erkrankungen des Gehirnes könnte höchstens die *arteriosclerotische Hirnatrophie* vielleicht noch in Erwägung kommen. Allein diese Krankheit hängt mit Blutungen, mit haemorrhagischen Herden innig zusammen und kann mikroskopisch mit der Negrolethargie wohl nicht verwechselt werden.

Wenn hier *über den Zusammenhang der klinischen Beobachtungen und der pathologisch-anatomischen Befunde* die Rede geht, so sei von vornherein bemerkt, dass es sich hier nur um die Erklärung einzelner klinischer Erscheinungen im Allgemeinen und nicht im Besonderen handeln kann, da ja einerseits erschöpfende Krankengeschichten nicht vorliegen, andererseits jedoch nur Bruchstücke des Leichenmaterials zur Verwendung stehen. Auch sei gleich erwähnt, dass für die weitaus grösste Mehrzahl der vielfältigen klinischen Symptome bei Negrolethargie noch keinerlei pathologisch-anatomische Veränderungen nachgewiesen sind. Da

¹ Eine gewisse, wenigstens histologische Ähnlichkeit besitzt die Negrolethargie mit der *multiplen disseminierten Sclerose* des Gehirnes. Bei dieser wird die Rinde auch verhältnismässig geschont und im Marke sind ausgedehnte Gebiete zu sehen, in welchen ganz fern von den neugebildeten Gliawucherungsherden eine diffuse Vermehrung der Glia bei erhaltenen, ja man möchte fast sagen, unversehrten Markfasern stattfindet. Nur der Ähnlichkeit halber wird dieses Verhalten der Glia bei der multiplen Sclerose hier angeführt und nicht wegen der differenzialdiagnostischen Schwierigkeiten, denn die Unterscheidung zwischen beiden Krankheiten kann ja schon makroskopisch ganz leicht gemacht werden. Mikroskopisch zeichnet sich die multiple disseminierte Sclerose auch dadurch aus, dass die Gliazellen selbst eine viel schärfere Umgrenzung zeigen als bei Schlafkrankheit und in stark vermehrtem Masse Weigertsche Fasern bilden.

aber die Anschauungen von Mott und mir in einzelnen Punkten von jenen, welche in den Rapports der Portugiesen niedergelegt sind, abweichen, sei auch diesem Capitel einige Aufmerksamkeit gewidmet.

Um die obige Reihenfolge der angeführten Krankheitserscheinungen auch hier einzuhalten, sei gleich bemerkt, dass wir uns das Erhaltenbleiben aller körperlichen Sinnesempfindungen bis zum Ende am einfachsten dadurch erklären, dass eben das Parenchym der Nervensubstanz, weniger denn das Zwischengewebe von der Krankheit geschädigt wird. Aus dem gleichen Grunde lässt sich auch das Verhalten der Reflexe erklären, welche nach einer leichten Steigerung zu Anfang der Schlafsucht in der Regel bis zum Endstadium vorhanden sind und auffällig schwere und asymmetrische Störungen, so zu sagen, nicht aufweisen. Dieses Verhalten treffen wir bei allen Hautreflexen und ein ganz ähnliches bei den Pupillen. Über das Muskelzittern, sowie über die Abnahme der Muskelkraft und über örtliche Muskelsteifheit kann so lange nichts Bestimmtes mitgeteilt werden, bis nach vorausgegangener pünktlicher und vollständiger klinischer Beobachtung das ganze Cerebrospinalsystem zur histopathologischen Untersuchung gelangt. Dann erst wird man in die Lage kommen zu entscheiden, ob die von den portugiesischen Expedition mitgeteilte Abnahme der Kraft in den Beinen lediglich auf statischer oder aber auf histopathologischer Grundlage beruht; dann wird auch klargestellt werden, welche pathologischen Veränderungen für die Verkrümmungen des Rumpfes infolge ungleicher Spannung der Muskulatur verantwortlich gemacht werden können. Es wird von den Schlafkranken berichtet, dass sie die Neigung haben, stets nach einer Seite hinzufallen. Dieses Stürzen stets nach derselben Seite hin kann wohl nicht allein auf Muskelschwäche zurückgeführt werden, wie das in den Rapports der Portugiesen geschieht, sondern es wird, wie Mott behauptet, diese Erscheinung wohl mit grösster Wahrscheinlichkeit in den schweren Veränderungen um und im Kleinhirn die richtige Erklärung finden, ebenso wie auch das Taumeln als cerebellare Störung und nicht als Muskelschwäche aufgefasst werden

muss. Alle übrigen klinischen Beobachtungen wie z.B. die in den Rapports mitgeteilten¹ Erscheinungen von Monoplegie und Hemiplegie werden erst dann auf die richtigen histologischen Veränderungen und auf ihre wahren Ursachen zurückgeführt werden können, wenn man einmal in der Lage ist, in einem und demselben Falle nebst genauer Feststellung der klinischen Symptome auch die genaue mikroskopische Untersuchung vorzunehmen.

Das wichtigste *psychische Symptom*, die Schläfrigkeit und die nachfolgende unüberwindliche Schlafsucht haben ihren Grund wohl bestimmt in dem gesteigerten intracraniellen Drucke, wofür nach früheren Darlegungen mehrere und hinlängliche Ursachen vorliegen. Von besonderer Wichtigkeit ist der Umstand, dass in den portugiesischen Rapports unter den 70 beobachteten Fällen nur über einen einzigen Kranken von psychischer Schwäche berichtet wird, während über alle anderen Kranken die Mitteilung kommt, dass sie die geistigen Fähigkeiten nicht verlieren, sondern nur träge und zum Denken unaufgelegt werden. Diese Tatsache allein legt die gründliche Verschiedenheit der Schlafkrankheit von der progressiven Paralyse dar. Eine charakteristische, tiefe Verblödung, ähnlich wie bei Paralyse, ist weder von den Engländern noch von den Portugiesen (wenn man bei letzteren vom erwähnten Falle absieht) bei den Schlafkranken wahrgenommen worden, was seine Erklärung wiederum nur darin finden kann, dass die histopathologischen Veränderungen bei der Negrolethargie weit mehr in der Neuroglia als im Parenchym vor sich gehen.

Die Färbemethode, deren ich mich bediente, beruht in einer Umänderung der Malloryschen Axencylinderfärbung. Durch Behandlung der Schnitte mit Gerbsäure werden einerseits die Axencylinder abgebleicht, während andererseits die Glia deutlicher sichtbar gemacht wird.² Das Genauere hierüber wird demnächst in einer deutschen Zeitschrift voraussichtlich in der Monatschrift für Psychiatrie und Neurologie veröffentlicht werden.

¹ Und lediglich aufgesteigerten, örtlichen Druck zurückgeführten.

² Die gefärbten Schnitte werden durch 5 Minuten gebleicht in einer Lösung von: Gerbsäure 40·00 und 50 procentigen Alkohol 100·00 Gramm; sodann aufgeheilt in folgender Lösung: Picrinsäure 1·5 und 50 procentiger Alkohol 100·00.

Es obliegt mir noch die angenehme Pflicht, Dr. Mott, dem Director des Laboratoriums der London County Asylums zu Claybury, für die Ueberlassung des Materials und für die Förderung meiner Arbeit, sowie dem Landesausschusse von Tirol für die Gewährung eines Urlaubs zu wissenschaftlichen Studien meinen verbindlichsten Dank auszusprechen.

ANHANG.

Dasjenige, was Mott in seinen "histological Observations on Sleeping Sickness and other Trypanosome Infections" (from the Pathological Laboratory of the London County Council Asylums, November, 1906, Seventh Report of the Sleeping Sickness Commission Royal Society), über die Schlafkrankheit berichtet, soll zur Ergänzung meiner Beobachtungen hier in gedrängter Form mitgeteilt werden.

Nach der Überzeugung von Mott steht es fest, dass die Schlafkrankheit hervorgerufen wird durch das Trypanosoma Gambiense, welches durch eine Beissfliege, Glosina palpalis, eingimpft wird.

Die Krankheit ist charakterisirt durch eine chronische Polyadenitis, welche gefolgt ist von chronischen entzündlichen Veränderungen der Lymphgefässe des Gehirns und des Rückenmarkes.

Die chronischen Veränderungen des Nervensystems bestehen in einer Vermehrung und Vergrösserung der Neurogliazellen, besonders jener, welche in Beziehung stehen zum Subarachnoidealraum und zu den perivascularären Lymphräumen, mit einer Anhäufung von Lymphocyten im Netzwerk der Glia. In chronischen Fällen kann man ausserdem Plasmazellen von Marschalko beobachten. Verschiedene andere Zellen werden in geringer Anzahl gefunden, Zellen, wovon einzelne das Ergebnis von degenerativen Veränderungen, andere endothelialen Ursprunges sind und phagocytäre Eigenschaften besitzen.

Die meningeale und perivascularäre Gliazellenwucherung und Lymphocyten proliferation und Infiltration des Centralnervensystems kann man als das Ergebnis eines chronischen reizenden Processes auffassen im ursächlichen Zusammen-

hang mit dem Vorhandensein von Trypanosomen in der Cerebrospinalflüssigkeit.

Die Untersuchung von Strichpräparaten, hergestellt von frischem Saft der Lymphdrüsen, den man bei Lebzeiten entnommen und auf Trypanosomen gefärbt hat, beweist mit Bestimmtheit, dass die Ursache der Drüsenerweiterung und der chronischen entzündlichen Veränderung derselben im Vorhandensein der Trypanosomen gelegen ist. Wenn man von dieser Tatsache ausgeht und im weiteren noch beobachtet, dass in den perivaskulären und meningealen Zellanhäufungen ebenfalls Trypanosomen vorhanden sind, so ist man berechtigt, auch hier die Trypanosomen als Ursache der Erkrankung anzusprechen. Tatsächlich können in beiden Fällen, sowohl an Strichpräparaten von frischem Gehirn, wie an solchen von Lymphsaftdrüsen, manchmal Trypanosomen gefunden werden. Überdies haben die Veränderungen, welche in den Lymphdrüsen gefunden werden, auch sonst in mancher Beziehung Ähnlichkeit mit den infiltrierten Stellen der perivaskulären Lymphräume des Centralnervensystems. In letzteren finden sich ähnlich wie in ersteren vermehrte Lymphocyten, Körnchenzellen, Plasmazellen, gewucherte Endothelzellen, Zuweilen veränderte Trypanosomen und zahlreiche Chromatinschollen, all'das ist eingeschlossen von einem Balkenwerk mächtig gewucherter Neuroglia.

Da alle Fälle von Schlafkrankheit gelegentlich in der Cerebrospinalflüssigkeit Trypanosomen zeigen, so ist es wahrscheinlich, dass ihre Einwanderung in diese Flüssigkeit den Beginn der Krankheit bedeutet und dass sie allmählig die chronische entzündliche Veränderung des Lymphgefäßsystems im Gehirn und Rückenmark verursacht. Eine andere Annahme geht dahin, dass die Trypanosomen durch ihre Vermehrung in den Lymphdrüsen ein Toxin erzeugen, welches von den Lymphgefäßen aufgenommen wird. Dieses Toxin schreitet hauptsächlich von den Cervicaldrüsen her durch die Lymphstränge der grossen Gefässe und Nerven in die Schädelhöhle und gegen das Centralnervensystem vor.

Aus den weiteren Beobachtungen geht hervor, dass die

Veränderungen im *Nervengewebe* bei Negrolethargie von denen bei Paralyse verschieden sind. Bei dieser liegen die primären Veränderungen im Parenchym und die secundären im Zwischengewebe, und bei der Schlafkrankheit finden sich umgekehrt die primären Veränderungen im Zwischen-gewebe, während die Veränderungen des Parenchyms erst secundär auftreten. Es handelt sich demnach bei der Schlafkrankheit primär um eine chronische Entzündung der Lymphwege mit mächtiger perivascularer Gliawucherung im Centralnervensystem. Die dadurch hervorgerufenen Gliawucherungen gehen den Veränderungen im Parenchym weit voraus und unterscheiden sich daher wesentlich von den Veränderungen bei progressiver Paralyse.

Es wäre natürlich nicht ausgeschlossen, dass andere Mikroorganismen die Schlafkrankheit verursachen könnten, das ist indes nicht wahrscheinlich, weil man nicht weiss, in wie weit die Infection der Lymphdrüsen mit *Diplostrep-tococci*, die ja auch vielfach bei Schlafkranken gefunden werden, Toxine erzeugen kann, ohne allgemeine Pyaemie zu verursachen, und inwieweit dadurch chronische Veränderungen im Lymphgefässsystem hervorgerufen werden können.

Ferner berichtet Mott in den *Proceedings of the Royal Society, B*, vol. 78, 1906, über einen Fall von *Dourine* oder *Mal de coit beim Pferde* und Vundvergleicht die dabeigemachten Beobachtungen mit den bei der Schlafkrankheit gefundenen, März 8, 1906 :

Dr. Eisath worked during the month of December, 1905, in the Pathological Laboratory at Claybury. A summary of his observations on the "Changes in the Neuroglia in Sleeping Sickness" was published as an addendum to the "Histological Observations in Sleeping Sickness and other Trypanosome Infections," by F. W. Mott, M.D., F.R.S., Report No. VII. of the Sleeping Sickness Commission of the Royal Society, December, 1906. For the benefit of English readers this is subjoined.

(1) *The character of the glia cells and their differentiation from lymphocytes.*—(a) The nuclei of the glia cells almost universally show a distinct nuclear membrane and possess normally two to three nuclear bodies, besides other

small granules. The leucocyte nuclei are of many forms; some are round and possess an abundance of granules, others are lobulated and have an indistinct outline.

(b) The glia nucleus forms quite one-third of the transverse diameter of the cell, whilst the nucleus of the leucocyte fills up the greatest part of the cell. That is to say, the glia cell has a relatively much larger proportion of cell protoplasm than the leucocyte.

(c) The protoplasm of the glia cell is arranged in a star-like manner around the nucleus; and the border of the cell, in normal conditions, is very distinctly seen, whilst in the leucocytes it is not.

(2) *The distribution and localisation of the glia proliferation.*—The glia overgrowth is demonstrable in every case and the cells are both increased in numbers and size. Giant glia cells were observed, and in every case the Weigert fibres are increased.

In the molecular layer of the cortex of many cases the glia cells are increased and often show an abundant formation of Weigert fibres, especially around the vessels. In the Meynert ganglion cell layers the increase of glia cells is relatively much less developed than in the superficial layer of the cortex, and in the white substance. The Weigert fibres, moreover, are only sparingly seen. In one case (Kirongo) the fibre formation is hardly demonstrable, and glia cells with surrounding protoplasm and processes are hardly recognisable in the cortex. The glia overgrowth in the white substance is, however specially observable around the larger vessels. *It exists not only around those vessels which show leucocytic infiltration, but also around capillaries where infiltration with round cells has not occurred.*

In the medulla oblongata the overgrowth and the morbid changes are most extensive.

In the spinal cord an extensive overgrowth of glia tissue exists by which the individual nerve fibres are surrounded, and this overgrowth affects all the tracts as well as the grey matter. There is no appreciable outfall of the medullated fibres, *only here and there and quite*

sparsely have the medullated fibres disappeared. The glia cells are numerically increased and increased in size beyond the normal.

(3) *Pathological changes in the glia cells.*—The glia granular substance was not precisely investigated in this work and shows, so far as the researches extend, in the round glia cells *no marked pathological changes.*

Isolated glia cells possess well-developed protoplasmic processes, others enormously increased Weigert fibres. Some of the glia cells have a uniform *homogeneous stained protoplasm* as if the nuclear substance had dissolved out or had disappeared.

Such cells usually have a dark brown stained nucleus, whilst others may have lost their processes and are converted into *hyaline balls.*

LITERATURANGABEN :

- Alzheimer, *Arch. f. Psychiatr.*, 1897.
 Derselbe, "Histolog. und Histopathologische Arbeiten," Nissl's B. I.
 Derselbe, *Monatschrift für Psychiatr. und Neurolg.*, B. II.
 Bruce, angeführt nach Mott, *Brit. Medical Journ.*, XII.
 Castellani, *Journ. of Tropical Med.*, June, 1903.
 Dercum, *The Journ. of Nerv. and Ment. Disease*, February, 1903.
 Evensen angeführt nach *Jahrbücher f. Psych.*, 1901.
 Guerin, "La Maladie du Sommeil," These de Paris, 1889.
 Held, *Abhandl. d. Sächs. Gesellsch. d. Wissensch.*, B. 28, 1904.
 Holschewnikoff, *Virchow's Arch.*, B. 112, 1888.
 Kromayer, Dissertat., Bonn, 1885.
 Liebmann, *Jahrbücher f. Psych.*, B. 5, 1884.
 Derselbe, *Proceedings of the Royal Society*, B. vol. 78, 1906.
 Manson, *Brit. Medical Journ.*, 1903.
 Mott, *Brit. Medical Journ.*, 1899.
 Derselbe, *Brit. Medical Journ.*, 1903.
 Derselbe, *Proceedings of the Royal Society*, B. 76, 1905.
 Derselbe, *Proceedings of the Royal Society*, B. 78, 1906.
 Nissl, *Archiv. für Psychiatr.*, B. 86.
 Rapports, "La Maladie du Sommeil, der portugiesischen Forschungs Expedition" (Bettencourt, Kopke, de Recende und Mendes), 1903.
 Sarmento e França, *Revist Portug. de Med. e Cirurg. Pr.*, VI., 1901.
 Valente, Disertação inaug., Lissabon, 1902, angeführt nach den Rapports.
 Ziegler, "Lehrb. der Allg. Pathologie Pathol. Anatom.", 1901.
 Ziemann, *Centralblatt für Bacteriolog.*, B. XXXII

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